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1788
Nutrition in oph..

Nutrition
in
Ophthalmology

By
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Contents

PAGE

PREFACE ... iii

CHAPTER I—Conjunctiva, Cornea and Sclera ... 1
  Vitamin A Deficiency ... 1
  Ariboflavinosis ... 16
  Amino Acid Deficiency ... 40
  Keratoconus ... 44
  Interstitial Keratitis ... 45
  Spring Catarrh ... 47
  Sjögren's Syndrome ... 49
  Myopia ... 51
  Vitamin Treatment of a Variety of Corneal Diseases ... 53

CHAPTER II—Lens and Aqueous ... 56
  Vitamin C in Ocular Biology ... 56
  Vitamin C in Ocular Pathology ... 65
  Cataract and Riboflavin ... 75
  Cataract and Amino Acids ... 82
  Cataract and Carbohydrates ... 84

CHAPTER III—Retina, Optic Nerve and Visual Act ... 88
  Night Blindness ... 88
  Role of Riboflavin in Vision ... 101
  Diabetic Retinopathy ... 104
  Diseases of the Optic Nerve ... 106
  Vitamin K in Ophthalmology ... 118
  Central Nervous System ... 120
  Vitamin P, Hesperidin, Rutin in Ophthalmology ... 122
  Niacin in the Treatment of Eye Conditions ... 126

APPENDIX: Reviews on Vitamins in Ophthalmology not quoted in Bibliography ... 129

SUBJECT INDEX ... 130

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Preface

In 1948, twenty-seven staff members of the Massachusetts Eye and Ear Infirmary in Boston received a questionnaire, prepared by V. E. Kinsey, asking how many of the 30,000 patients whom they had seen during the previous year had ocular signs caused by, or associated with, improper diet. Ten members of the staff replied that they had not encountered any eye disorders due to malnutrition, the others had seen 17 cases altogether, representing 0.06 per cent of the total. Most of these patients suffered from rosacea keratitis, which was listed but the nutritional etiology of which was doubted, or toxic amblyopia. Two patients had keratomalacia.

This reticent attitude towards acknowledging the importance of nutritional deficiencies in the causation of ocular signs and symptoms is representative of the great majority of the profession. It is caused by several factors, the most prominent ones being the natural reluctance to accept new concepts before they have found a solid foundation and backing and the fact that the publications treating the relation of nutrition to vision and the eye are scattered widely in the literature. The sections on vitamin deficiencies in ophthalmological text books, with the rapid progress made in the past years, are necessarily out of date by the time they appear. The authoritative text books on vitaminology give ophthalmology only a small share of their space and even then matters of interest to the ophthalmologist are distributed in small parcels over many chapters.

Nutritional deficiencies should be the concern of the ophthalmologist to as great an extent as of the practitioner in any other branch of medicine. They affect the eye directly and indirectly and, although not too much is known of the effects of chronic or mild deficiency, it is quite likely that the eye will prove to be one of the best indicators of the presence and importance of a number of such deficiencies.

From my many contacts with eye specialists of high professional standing, I have received the impression that vitamin deficiencies in their relation to the eye are still regarded by many as in the domain of drug stores and popular magazines. It is hoped that this attempt to collect the material available as completely as possible, to sort it out and review it critically, will result in a useful reference work for the practicing ophthalmologist as well as for those engaged in research and teaching in nutrition and in ophthalmology.

While conservatism and doubt are the mainstay of sound medicine, it is just as true that curiosity is the mother of progress. If this monograph succeeds in arousing the curiosity of some and in allaying the doubts of others, it will serve its purpose. As with all review articles of its type, the very latest information is not included and must be looked for in current periodicals; the literature of the year 1949 is but incompletely covered.

It is a deep satisfaction for me to be able to express here, however inadequately, my sincere gratitude to Dr. Norman Jolliffe, who freely offered opportunity and advice without which this monograph would not have been written, and to Dr. Robert S. Goodhart, whose constant encouragement and help were of immeasurable value. My thanks are also due to the members of the Scientific Advisory Committee of the National Vitamin Foundation, particularly to Dr. H. D. Kruse, for their suggestions and editorial work.

J. J. STERN.

Chapter I

CONJUNCTIVA, CORNEA AND SCLERA

VITAMIN A DEFICIENCY

Signs and Symptoms

The epithelial changes in the eye due to vitamin A deficiency have been known for a long time. There is a wide margin between simple xerosis conjunctivae and the fully developed picture of keratomalacia with its destruction of the cornea and eventual blindness. The latter type is hardly ever seen any more in civilized countries. Xerosis is more frequent, particularly in undernourished infants, where improper diet after cessation of breast feeding is a common cause of its appearance (1). Liver disease, particularly in infants who have not yet accumulated stores of vitamin A in the liver, may be a factor in the production of xerosis or even of keratomalacia because the diseased organ may be unable to change carotene into vitamin A or to store or mobilize vitamin A. The occurrence of clinical vitamin A deficiency in the presence of liver disease has been observed recently by Houet and Weekers (51) in two twin infants; both were similarly fed, but one developed jaundice, xerosis and keratomalacia while the other showed no affection of the liver or the eyes.

In xerosis conjunctivae, the bulbar conjunctiva presents a peculiar dry aspect, described as "lack of lustre". Light reflection from the conjunctiva is interfered with. This becomes easily detectable when the lids are kept open for 10 or 20 seconds. In the very early stages, the conjunctival changes are patchy, becoming confluent when the condition progresses. The deeper conjunctival and episcleral vessels take on a bluish tinge or become invisible because of the diminished transparency of the epithelium. Loss of elasticity causes a wrinkling of the conjunctiva which can be provoked by pushing the bulbar conjunctiva towards the limbus with a finger pressed over the lower lid. Later the folds appear spontaneously, forming concentric circles and showing dry, lusterless tops and moist furrows when the eyes are moved sideways.

Another common sign is the appearance of Bitôt's spots: white, elevated, sharply outlined patches not wetted by tears and covered with material resembling dried foam. They are usually triangular in shape, the base of the triangle facing the limbus, and most frequently occupy the temporal side of the conjunctiva, within the lid aperture. The foamlike substance can be scraped away but reforms. It consists of epithelial debris, fatty globules and frequently masses of xerosis bacilli. The latter were regarded at one time as the causative agent of conjunctival xerosis, but it is clear now that they are but saprophytes and have no diagnostic or etiologic significance.

In the Orient, an additional sign of xerosis has been described in the form of a certain type of conjunctival pigmentation (2-8). Matsuoka regards it as one of the first signs of avitaminosis A and ascribes it to an increased production of melanin, due to metabolic disturbances in the epithelium. Most other observers have seen it only after other signs of xerosis had been present for some time. The pigmentation is described as first occupying the lower part of the conjunctiva bulbi, the lower fornix and the semilunar folds; these areas become yellowish, then gray, finally bluish mauve. Later on, the same changes may appear in the upper lid and fornix. Pillat has shown the pigment to be melanin. It usually remains for some time after all other evidence of the disease has responded to therapy but is claimed to yield eventually to vitamin A treatment.

A smoky discoloration of the bulbar conjunctiva, attributed to vitamin A deficiency, has been described in colored races. It has been shown to be due to an outward migration of chromatophores from the limbal pigment ring (9). The same phenomenon has been produced experimentally in rabbits fed a diet deficient in Vitamin A. Only animals with pigment showed it: there was no development of new chromatophores (10).

This pigmentation seems to occur only in the colored races, or in individuals with dark complexions, where pigment is physiologically present in the conjunctiva. It seems possible that in some instances a physiological pigmentation has been mistaken for a pathological condition.

In severe cases of xerosis all signs are augmented. The bulbar conjunctiva becomes thick, opaque, thrown into large folds and furrows. At the same time the cornea becomes involved. The first signs here have been described as loss of luster, dryness when exposed to air and reduced sensitivity (4,7). This latter sign may be significant as it suggests nerve involvement and will be discussed later. When the condition progresses unchecked, patchy areas resembling Bitôt's spots appear on the cornea, sometimes as a prolongation of conjunctival spots; sometimes as crescents along the limbus, and occasionally as isolated areas in the center. If the condition advances further, true keratomalacia sets in. The cornea becomes dull, central or peripheral infiltrates form and the periphery becomes vascularized. The epithelium over the infiltrates is shed, the ensuing ulcers undergo infection and the cornea finally perforates. The vascularization of the cornea in these cases is morphologically different from that seen in riboflavin deficiency and may be secondary to the necrosis of the corneal epithelium.

Vitamin A deficiency has been accused of responsibility for the follicular conjunctivitis frequently seen in otherwise apparently healthy children. There is no convincing evidence that this is the case. Follicular conjunctivitis or conjunctival folliculosis has been called by French authors a "waiting room" for a group of conditions about which little is known and which have one sign in common, the conjunctival follicles. Duke-Elder calls it a convenient scrap-heap and points out that the conjunctiva tends to react to irritation of any kind by lymphatic hyperplasia and the formation of follicles, like all other adenoid tissue. Follicle formation is a common reaction and by no means distinctive (11).

Kruse (27) stirred up considerable interest with his publications concerning pigmentation and the occurrence of conjunctival spots, regarded by him to be due to chronic vitamin A deficiency, in a large number of seemingly healthy subjects. Out of 143 persons in a low income group, 45% had gross and another 54% microscopic ocular lesions "characteristic of avitaminosis A". The spots are described as "grossly perceptible elevated conjunctival spots of distinctive color and characteristic location". The pigmentation is "creamy, ivory, taupe, greenish-white, whitish-green, bluish-milky, yellowish-orange, gray-brown with underlying whitish-green, greenish-yellow, amethyst, silvery and galena". Kruse observed these lesions to disappear in 9 persons and to recede in all the others when treated with vitamin A. A striking feature was the very long period of time required for complete recovery, a matter of months even with very big doses —100,000 units daily. Control subjects who did not receive treatment failed to show improvement. Kruse found in the entire group only a few high adaptometer readings, and not all persons with "advanced xerosis" showed high levels—nor were high levels restricted to those with the most pronounced "xerosis". He argues that xerosis probably precedes night blindness as an early sign of vitamin A deficiency.

Kruse has found severe critics. It is unlikely that gross anatomical lesions such as pigmentation and spots would appear earlier than disturbances of the very delicate light sense. Functional disturbances usually precede anatomical changes (28). It has been argued that the states seen by Kruse are not prexerosis but common senile or presenile alterations. This may be the case, but one must admit that such senile alterations really might be due to chronic mild vitamin A deficiency and not be physiological signs of old age. Much more pertinent is the criticism that the spots described by Kruse are most probably pingueculae, which are subepithelial and do not involve the epithelium where vitamin A deficiency shows itself (29). Kruse, in his reply (52), pointed out that in his cases the pinguecula never was the only change in the conjunctiva, and that many of the "spots" seen by him were more like Bitôt's spots. Actually, he asserts, "no one term of the past used with histologic connotation would be satisfactory". He is convinced that all the various conjunctival changes described by him are but several manifestations of different degrees and stages of avitaminosis A. Berliner's criticism that Kruse's spots are subepithelial while avitaminosis A manifests itself in the epithelium alone is, in Kruse's opinion, inadmissible. The subepithelium has been shown to be involved (53), even in acute animal experiments, and must be expected to be subject to more changes in chronic deficiency states.

Another discordant fact is that most subjects with positive slit lamp findings had normal vitamin A values in the blood. Berliner also criticizes Kruse's method for the estimation of the thickness of the conjunctiva and reminds us that prexerosis, xerosis and Bitôt's spots are not always due to vitamin A deficiency but may be caused by conditions like pemphigus or trachoma scars.

Whatever the value of Kruse's observations, it must be pointed out that a total lack of correlation between the dietary intake of vitamin A or blood levels of vitamin A and conjunctival changes has been observed (30, 31). Robertson and Morgan (32) examined 40 pupil nurses of between 19 and 26 years of age. They divided them into three groups, the first of which consisted of 15 subjects with clear conjunctivae; the second, of 13 subjects with somewhat opaque conjunctivae (8 of which showed pingueculae), and the third of 12 girls with more opaque conjunctivae, 10 showing pingueculae. All subjects were on good diets. One half of each group received 50,000 units of vitamin A daily, the other half a placebo. The authors did not know to which half the subjects belonged when they examined them again two years later. After this prolonged and intensive treatment no significant changes in the state of the conjunctiva were observed. Kruse (50) objects that the method of recording used by Robertson and Morgan would not permit them to detect recession of pathology.

Ida Mann and co-workers (10) experimented with rabbits in which vitamin A deficiency was induced. They could not produce any spot lesions in the conjunctiva and present their findings as opposed to those of Kruse; they admit, however, that there might be differences in the development of xerophthalmia between man and rabbit. In man, Ferguson (48) reports that deprivation of vitamin A over a period of 25 months caused a drop in the carotenoid and vitamin A content of the plasma, but no changes in the degree of opacity of the conjunctiva that were not found also in controls. The most recent and probably most comprehensive experimental work done on human volunteers was published by The Medical Research Council of Great Britain in 1949 (49). The results reported by this team are the same. No conjunctival or corneal changes occurred after up to 25 months of vitamin A depletion in spite of an early drop in the carotenoid level of the blood and a drop of the vitamin A level after about 8 months in some of the subjects.

While the diagnostic value of certain signs is still *sub judice,* there can be little doubt but that thickening of the conjunctiva is one of the early signs of xerosis. This has been confirmed again lately in the revealing statistical surveys of nutrition in Newfoundland by Aykroyd, Jolliffe, Lowry et al (41). On page 15 of their report the following occurs: "The occurrence of thickening of the conjunctiva was very high in Newfoundland in 1944. Such thickening is commonly observed in adults everywhere. It is, however, generally uncommon in children. One of us (Wilder) compared its recorded prevalence in the 402 children of grade school age in the Newfoundland sample of 1944 with that observed in an examination of some 300 Minnesota children. The prevalence was over 70% in Newfoundland and only about 4% in Minnesota. The causes for this abnormality are not known, but in the 1944 survey a significant correlation was demonstrated in the youngest age groups (5-10 years) between serum vitamin A levels and this lesion. Improvement with respect to it, in Newfoundland, is apparent from the statistically significant change in frequency of occurrence between 1944 and 1948." The changes which took place in Newfoundland in the diet between 1944 and 1948 consisted of the fortification of all margarine with vitamin A and the enrichment of bread.

In regard to corneal vascularization, this sign has been observed in rats with more advanced lesions of avitaminosis A as a regular occurrence (20, 33). Ida Mann and co-workers were unable to obtain it in rabbits (10). It is considered by Bessey and Wolbach (33) to be a secondary reaction of the limbic plexus to serious alterations of the corneal tissue associated with infection.

Pathology

The mechanism of the epithelial damage in vitamin A deficiency is by no means clear. The occurrence of tissue changes has not been related to the distribution of vitamin A in the tissues, nor does the order in which the various organs are affected give any indication of the fundamental principles involved. Anatomically the changes can be described as "atrophy of the epithelium, reparative proliferation of the basal cells and growth and differentiation of these new products into a stratified keratinizing epithelium" (Wolbach) (14). Before any evidence of xerosis is present, the goblet cells can be observed to disappear and hyaline degeneration to occur in the protoplasm of the epithelial cells (12). Later on, the epithelium is thickened, the superficial cells become flattened and lose their nuclei, and prickle cells appear in the deeper layers. The more superficial cells form lamellae which stain diffusely as kerato-hyaline; the cells underneath show granules of the same material (13).

In general the epithelial structures which atrophy and become replaced by stratified keratinizing epithelium are those which have a secreting function in addition to the role of a covering layer, and whose functioning cells are without power to divide: the epithelium of the respiratory tract, the salivary glands, the mouth and the tongue, the renal pelvis, ureter, bladder, and the conjunctiva are affected. During recovery following vitamin A administration, the epithelium of each region returns to its normal morphology and function.

Friedenwald and his associates (15) found the mitotic rate of a healing corneal wound in an avitaminotic A rat to be reduced by 30%, and also observed an inhibition of speed of the mitotic cycle. They therefore denied the augmented growth of the metaplastic epithelium claimed by Wolbach.

An interesting contribution has been made by Mellanby (16) who considers the condition to be essentially neurotrophic. In experimental xerophthalmia he observed degenerative changes in the myelin sheath of the trigeminal nerve. In early cases, where the epithelium returns to normal on the addition of vitamin

A or carotene to the diet, the nerve also returns to normal; in more advanced cases typical Wallerian degeneration takes place and similar degenerative changes can be found in the cells of the Gasserian ganglion. These findings are particularly interesting in view of the clinical observation of reduced corneal sensitivity in xerosis, and Pillat's (17) slit lamp findings of thickened corneal nerves at an early stage of the disease. In an autopsy of a clinical case, Circincione (18) found degeneration of the cells of the Gasserian ganglion and the ciliary ganglion. We shall encounter later on important studies and observations concerning nerve involvement in the development of embryos whose mothers are deprived of vitamin A, and of nutritional factors playing a role in the optic atrophy of tabes. Taken together, these varied facts may indicate some importance of peripheral nerve involvement in the pathogenesis of xerophthalmia.

Ida Mann and co-workers (10), in controlled experiments, succeeded in elucidating the precise time relationship between the various clinical signs and their relation to the vitamin A level in the blood. The test animals were rabbits, 50 of which were fed on a diet deficient in vitamin A while 10 were used as controls. Vitamin A deficiency was induced in two age groups: healthy weaned rabbits 5-7 weeks old and younger animals, the mothers of which were put on a vitamin A deficient diet soon after the birth of the young. When the deficiency signs had reached the desired stage, one eye was removed, examined histologically, and vitamin A therapy instituted. When the ensuing improvement was maximal, the animals were killed and the eyes and other organs examined histologically. The following sequence of events was recorded:

(1). The primary changes were epithelial. Up to 3 months before any changes were visible with the naked eye, the biomicroscope showed characteristic alterations of the corneal epithelium in which some surface cells had an opaque and slightly greasy aspect. In this stage the histological picture revealed metaplasia of the corneal epithelial cells into squamous and keratinized cells.

(2). Simultaneously, or slightly following this, the conjunctival pigmentation became altered and an outward migration of the chromatophores of the limbal pigment ring took place.

(3). This was followed by keratinization of the lower fornix. Changes in the lacrimal glands are not the cause of the corneal changes because the latter appear first. No abnormalities were seen in the substantia propria, the endothelium or the nerves of the cornea, nor was there any corneal vascularization. It is important to note that the plasma level of vitamin A had to sink to 10% of the normal before any eye changes became visible. It must be borne in mind, of course, that these animal experiments were acute ones, conducted with very little or no vitamin A in the diet. They cannot be considered to be analogous to what happens in man, with a diet inadequate in vitamin A over a long period of time.

Treatment with vitamin A brought about rapid cure, starting on the 4th day of therapy and resulting in complete recovery in 1-6 weeks. The conjunctival pigment was the last sign to disappear.

Other hypotheses attempting to explain the phenomenon of xerosis seem to have lost their validity.

Desiccation owing to a loss of lacrimal secretion has been suspected (19) because of the finding of shrunken lacrimal glands in experimental animals. Xerophthalmia, however, may occur clinically with the persistence of lacrimation (20). A loss of lysozyme in the tears has been suggested as the primary factor (21, 22, 23); and the view has also been advanced that the local inflammatory symptoms are primary and the keratinization secondary (24). None of these explanations is acceptable in the light of more recent knowledge.

Differential Diagnosis

The clinical picture of xerosis conjunctivae and of the more severe stages of xerophthalmia and keratomalacia is rather clearcut. Difficulties in the differential diagnosis are encountered rarely. A therapeutic test, in addition to determinations of the blood levels of carotene and vitamin A usually will decide the diagnosis.

For diagnostic purposes a "keratinization index" has been proposed (25), representing the ratio between nucleated and non-nucleated, keratinized epithelial cells in a conjunctival smear. The significance of this index is doubtful and the test has failed to be accepted generally.

Prevalence

While keratomalacia is practically unknown in economically sound communities where even simple xerosis probably is an uncommon occurrence, these conditions cause havoc in large areas of the Orient and other areas where severe malnutrition is prevalent (25a). One half of all children attending hospitals in the Philippines in 1940 had xerophthalmia; in the

Dutch East Indies, 4,000 children in half a million are blind, chiefly as a result of this condition (26). Kruse's findings of signs, regarded by him to be pathognomonic for avitaminosis A, in 99% of persons in a low income group in the United States has been discussed in the foregoing pages.

Treatment

(a) Preventive Treatment. The daily requirements for vitamin A have been worked out by using dark adaptation and its maintenance at normal values in volunteers fed on diets containing predetermined amounts of these substances. An allowance of 5,000 I. U. for normal adults, based on the studies of Booher (42), Blanchard (43) and Guilbert (44), has been adopted in the list of Recommended Daily Allowances (45). A downward revision of this figure has been suggested by Coward et al (46), but long-run experiments on animals suggest the advisability of relatively high doses in order to maintain the integrity of successive generations (47). A detailed exposition of the situation can be found in the "Recommended Dietary Allowances", published in 1948 by the National Research Council. The Medical Research Council of Great Britain (49) recommends 2,500 I. U. of vitamin A (or 7,500 I. U. of carotene) as a minimum maintenance dose.

(b) Curative Treatment. It seems established that deficiency signs make their appearance only if and when the body stores of vitamin A have reached a very low level. This stage may be reached earlier in small infants who have not been able to accumulate stores of vitamin A during the short span of their lifes. In order to replenish the depleted stores at a fast rate it is advisable to administer the vitamin in doses many times that of the maintenance requirement. It is therefore the general practice to give 25,000, 50,000 or even 100,000 I. U. daily, until results can be produced. Treatment has to be adapted to special conditions. Individuals with liver disease or intestinal disorders, for instance, are generally on very poor diets and often on diets low in fats. Frequently they have difficulty in the utilization of ingested fat and of carotene. In addition to correction of the diet and the oral administration of bile salts, it is advisable to substitute preformed vitamin A for carotene as a source of the vitamin in such situations.

Vitamin A and carotene have been used locally in a number of eye conditions. It was shown by de Rötth (38) that the local application of cod liver oil to one eye in keratomalacia of the rat had a general healing effect on both eyes, a fact which seems to point to some absorption of the substance. Locally applied oil without vitamin A had some healing effect, but on the treated eye alone. According to Stevenson (37) cod liver oil seemed to give good results when instilled locally after corneal injuries, but de Rötth (38) failed to observe any local healing effect on corneal abrasions in rabbits.

Instillations of an alcoholic solution of carotene (1 mgm in 10 cc of 5% alcohol) gave good results in superficial neuroparalytic and interstitial keratitis and Mooren's ulcer. In pneumococcal ulcer, no cure was obtained with this treatment, but it seemed to have an analgesic and calming effect (34-36). These results are attributed to the general chemical properties of carotene and not to specific properties of vitamin A. Carotene instilled in human and rabbits' eyes after corneal transplantation did not protect the transplant from opacity and vascularization (39).

Local therapy with vitamin A does not seem rational, and should be replaced either by systemic administration of vitamin A, if a deficiency is suspected, or by appropriate local treatment.

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ARIBOFLAVINOSIS

Corneal vascularization is probably the earliest and most regularly appearing sign of riboflavin deficiency. It was first described as a sign of riboflavin deficiency in rats by Bessey and Wolbach (1) and in man by Kruse, Sydenstricker, Sebrell and Cleckley (2). Indefinite ocular changes, however, were observed very much earlier by a great number of investigators of pellagra, a clinical syndrome associated with a deficiency not only of tryptophane and of niacin but of riboflavin and other members of the vitamin B complex as well. The best food sources of niacin, the absence of which from the diet is responsible for the major diagnostic signs and symptoms of pellagra, are important sources of other constituents of the vitamin B complex as well. It is a quantitative rather than a qualitative difference that determines the preponderance of one set of signs and symptoms over another. Many observations have shown that aniacinosis may be cured promptly by niacin while signs of ariboflavinosis remain or may move into the foreground only at this stage (3).

The existence of eye signs in pellagra was known as early as 1791, when it was mentioned by Soler, an Italian authority on pellagra. When research workers started to experiment on animals in order to elucidate the question of the pathogenesis of pellagra, many observed ocular changes. Goldberger et al. (4) mention that rats on a vitamin G deficient diet showed loss of hair around the eyelids. Vitamin G was, of course, the whole B complex minus thiamine. Other authors making similar observations were Salmon et al. (5), Findlay (6), Chick et al. (7), Thatcher et al. (8), Sherman et al. (9) and Bourne et al. (10). The signs were variously described as "ophthalmia", conjunctivitis, alopecia of eyelids, keratitis.

When riboflavin was isolated from the "vitamin B_2 complex" in 1935 by Harris and synthesized by Karrer and Kuhn in the same year, it became possible to bring some clarification into the hitherto involved state of affairs. Sebrell and Butler (11) were the first to recognize a pure riboflavin deficiency in man. They described typical signs: angular stomatitis, seborrheic changes of the skin of the nose, eyelids and ears, and in 1939 (12) added a most important sign, a glossitis different from that observed in pellagra. They also designed the universally accepted name of ariboflavinosis. It has been said that the *alpha privativum* is not appropriate in this case, as a complete deprivation of riboflavin in the diet would quickly cause death. Hyporiboflavinosis would certainly be more adequate, but also less euphonic; the term coined by Sebrell and Butler has become a household word, and it will maintain its place in medical terminology, with the tacit understanding that it represents an overstatement.

The first definite statement on the occurrence of ocular changes in human ariboflavinosis was made by Spies and his associates (13) who briefly mentioned "visual disturbances". Some months later, in their review on pellagra, beriberi and riboflavin deficiency in human beings, the same authors (3) amplified their previous statement: they described a syndrome consisting of "bulbar conjunctivitis, lacrimation, burning of the eyes and failing vision" which responded in some instances to riboflavin. But since in other instances they had previously found that similar lesions responded to carotene, they said that it was too early to interpret the observation. Later they decided that the ocular manifestations were those of ariboflavinosis (15). Sydenstricker and co-workers (14) saw a similar condition with conjunctivitis and photophobia in a riboflavin deficient patient, and observed the disappearance of these signs following riboflavin therapy. Corneal vascularization in man was recognized by Kruse, Sydenstricker, Sebrell and Cleckley (2) shortly after Bessey and Wolbach published their observations in rats. They stated that the first signs of ariboflavinosis are dilatation and proliferation of the limbic vessels, followed by superficial vascularization and interstitial keratitis. Other signs claimed to be due to ariboflavinosis were photophobia, dimness of vision, congestion of the sclera and abnormal pigmentation of the iris. Sydenstricker et al. were able to make these signs disappear in 47 cases by riboflavin administration. In 5 patients repeated successive improvement and relapse was induced by alternate periods of provision and withdrawal of riboflavin therapy. Then these investigators concluded that the signs were caused by riboflavin deficiency.

The ocular signs of ariboflavinosis thus having been established it was not long before a veritable spate of publications followed, all of them confirming and amplifying. Spies and his associates (15) investigated families of ariboflavinotic patients and found that other members of these families, including children, frequently showed similar signs. Street, Cowgill and Zimmerman (16) observed increased lacrimation in dogs with experimental riboflavin deficiency, a finding confirmed by Spies (17) in pet dogs of families in which ariboflavinosis was present. Shaw and Phillips (18), on the other hand found that dogs on a riboflavin deficient diet showed diminished tear production and assumed the presence of a lesion of the lacrimal gland. Other animals observed were pigs, where a clouding of the cornea was found in ariboflavinosis by Patek et al. (19).

Signs and Symptoms

In 1941, Sydenstricker (20) published a further paper summarizing the state of knowledge of ariboflavinosis. According to this authoritative statement, the objective signs include injection of the bulbar and palpebral conjunctiva and the fornix, circumcorneal injection, engorgement of the limbic plexus, vascularization of the cornea, superficial and deeper interstitial changes, sometimes diffuse, sometimes patchy, congestion of the sclera and the iris, in some cases frank iritis. The subjective symptoms were stated to include itching and burning, roughness of the eyes, photophobia, impairment of visual acuity. He concluded that keratitis is the principal ocular-lesion, and that the most common and earliest ocular sign is circumcorneal injection.

The other ocular manifestations of ariboflavinosis, taken together, are not less typical of the condition. Tired, hot eyes, asthenopia with itching and burning are the usual complaints, without objective signs of inflammation or refractive errors. The bulbar and palpebral conjunctiva are normal and there is no discharge. The discrepancy between the patient's complaints and the paucity of clinical signs is characteristic.

The other clinical signs of ariboflavinosis will help in establishing the diagnosis, when present, but they are not always present, even when there is pronounced ocular discomfort and they are by no means indispensable for the diagnosis of ariboflavinosis. Cheilosis (synonyms: cheilitis, angular stomatitis, perlèche) consists of rhagades and reddening of the corners of the mouth and fissuring and chapping of the lips. The lesions are frequently infected by saprophytic staphylococci. When due to riboflavin deficiency they clear up without local treatment under riboflavin medication. A second classical sign is glossitis. The color of the tongue is said to be typical—the condition has been termed magenta glossitis—but the clinical picture is frequently disturbed by the concurrent presence of a niacin deficiency. In many cases medication with riboflavin alone is not sufficient to make it disappear; only after niacin is added does the condition clear up. This is not surprising in view of the fact that an isolated riboflavin deficiency probably never occurs in man, riboflavin being found in the same articles of diet as many of the other members of the vitamin B complex. Another sign frequently observed is dyssebacia about the naso-labial fold, the nose, and the ears. Finally, inflammation and fissuring of the outer canthi has been described as an occasional occurrence in ariboflavinosis (79, 80).

Pathology

Eckardt and Johnson (21) observed "keratitis" and vascularization of the cornea in rats on a riboflavin deficient diet, and noted the special relationship. Bessey and Wolbach (1) not only observed and described this condition, but also conceived an explanation which has been accepted almost universally. According to these workers, corneal vascularization is to be regarded as a compensatory process bringing blood into closer contact with the deeper layers of the corneal epithelium when the cornea is suffering from riboflavin deprivation.

The corneal epithelium shows a surprisingly high metabolic rate while that of the stroma is relatively low (22-26). Bessey and Wolbach (1) confirmed this by examining the excised cornea with the Warburg respirometer. They found that the cornea utilizes ca. 4 cmm. of oxygen per hour per mg. dry weight; this is about half of that of the highly active liver and muscle tissues, and four times as much as cartilage which had been assumed to have a rate of respiration very similar to that of the cornea.

Riboflavin, as the phosphoric acid ester, in combination with adenylic acid, forms a flavin-adeninedinucleotide which is the prosthetic group of a number of enzymes, particularly Warburg's yellow respiratory enzyme. It acts as a dehydrogenase in anaerobic glycolysis, maintaining a process of anoxybiotic fermentation. Molecular oxygen takes two H atoms from it, which are converted in H_2O_2 and then into H_2O and O. In this transfer, the place of O can be taken by any other H acceptor. This mechanism is essential for the respiratory process of the cornea and other avascular tissues.

Stannus (27), in elaborating his hypothesis of ariboflavinosis causing a "capillary dysergia", seems to be the only author who does not accept this explanation. His argument is that riboflavin, being a highly photosensitive substance, is destroyed in the cornea by light, and he thinks it strange that nature should provide the cornea with riboflavin there to be destroyed by light. However, this objection is not valid as riboflavin is present in the ocular tissues in its co-enzymatic form which is unchanged in vivo or in vitro by sunlight (28). Bessey and Lowry (26) published very interesting studies on the riboflavin content of the cornea in riboflavin deficient rats. They found that bright light and ultraviolet irradiation fail to lower the riboflavin concentration in the living eye; they also confirmed the observation that the corneal epithelium contains 6-8 times as much riboflavin as the rest of the cornea.

Three days after the animals of Bessey and Lowry had been placed on a riboflavin-deficient diet, the riboflavin content of the cornea fell, first rapidly, then leveling off slowly after 3 weeks at 40% of the original value. If the rats were fed on a diet not completely deprived of riboflavin but containing less that the optimum, the decrease of riboflavin in the cornea was slower but eventually led to a level approaching the absolute deficiency level. Administration of riboflavin resulted in a prompt rise in the riboflavin concentration of the cornea. It is interesting that, in spite of the large amounts of riboflavin employed, the cornea never fully regained the riboflavin concentration of that of rats continuously maintained on a high riboflavin diet. This seems to indicate a lasting lesion of the corneal tissue, perhaps due to a loss of "acceptors" (flavin enzymes or cellular constituents). Another important finding by Bessey and Lowry is that deficiency signs appeared in the cornea only when the riboflavin concentration fell to less than half the normal value.

The oxygen consumption of the cornea of riboflavin deficient rats is lessened (25). When vascularization of the cornea is present, the oxygen uptake of the corneal stroma is elevated, in the absence of vascularization it is rather low. The increased oxygen uptake of the stroma must therefore be the result of the vascularization and perhaps of the cellular infiltration.

These physiological facts and experimental findings lead convincingly to the conclusion that riboflavin is essential for the respiration of the avascular cornea. In its absence the normal respiratory process of the cornea is profoundly disturbed, and attempts are made by the organism to substitute oxybiotic metabolic processes for the normal anoxybiotic ones by bringing blood into closer contact with the corneal cells. The result is the clinical condition of corneal vascularization.

Stannus (27) believes that the cornea receives riboflavin from the tears and the secretions of the Meibomian glands, a suggestion previously made by Philpot and Pirie (28) and Pirie (29). The lacrimal glands were shown by these workers to contain 6.5 micrograms of riboflavin per gram, but as far as can be ascertained the riboflavin content of tears has not yet been examined. The secretion from the Meibomian glands contains 4.0 micrograms of riboflavin per gram, twice as much as the corneal epithelium.

A peculiar fact observed in rats by Bowles, Allen, Sydenstricker, Hock and Hall (30) and also seen in man quite frequently by us is in support of Stannus. In 60% of ariboflavinotic rats, corneal vascularization took place first in the superior nasal quadrant. It is conceivable that this part of the cornea is the first to suffer because of its situation, the other three quadrants being more profusely irrigated by the tears. On the other hand, covering the cornea of riboflavin deficient rats with a water-repellent ointment and thus insulating the cornea from the action of the tears has failed to accelerate the vascularization of the cornea (31). It is doubtful whether this experimental procedure is absolutely effective in preventing the tears from coming in contact with the cornea. More damaging to Stannus' hypothesis is the fact that removal of the lacrimal and Meibomian glands does not produce corneal vascularization (28).

Differential Diagnosis

It is unfortunate that a number of workers picked some of the signs and symptoms of ariboflavinosis as described by Sydenstricker and his group out of the syndrome and accepted them as pathognomonic signs of ariboflavinosis. Circumcorneal injection is indubitably an early sign of this condition, but it occurs also in very many other ocular upsets. To expect riboflavin to exert a therapeutic influence on every case of circumcorneal injection was, of course, courting disappointment. Early enthusiasm was soon tempered by critical or frankly rejecting papers, and it took considerable time until factual observation, description and sorting out permitted the correct evaluation of the ocular signs and symptoms of ariboflavinosis.

Unmistakable corneal vascularity has been described by Bessey and Wolbach (1) and Kruse et al. (2). Much trouble could have been avoided if Sydenstricker and Kruse and their group had not included "conjunctivitis", "engorgement of the limbic plexus" and "circumcorneal injection" as early signs of ariboflavinosis, and if some of the subsequent workers had first made themselves familiar with the variations of the limbus as visualized by the slit lamp. Corneal vascularity is a condition in which *newly formed* blood vessels leave the limbic plexus and centripetally enter the subepithelial space of the true cornea. This state, and nothing less, is acceptable as corneal vascularity.

The limbus is not a line but a band about one millimeter wide, consisting of the wedge-shaped edge of the sclera which overlaps the corneal tissue, the cornea being inserted into the sclera like a watch glass. This area is plentifully provided with blood vessels which comprise the limbic plexus (32). The limbic plexus is not always visible in the living eye as the vessels frequently are empty and do not show. The plexus responds readily to mechanical or chemical irritation that causes conjunctival hyperemia and opens the vessels of the limbus. The state of filling of the limbic vessels may change from hour to hour, depending on light, wind, dust, accomodative strain, etc.

Hyperemia of the limbic plexus is entirely nonspecific. The sprouting out of new vessels from the limbic plexus is preceded by engorgement and increased activity of the plexus itself. This condition will or will not respond to riboflavin administration, according to its etiology. For practical clinical purposes it must be insisted upon that vessels must appear in the cornea before one can speak of corneal vascularity. The importance of a correct anatomical diagnosis has been emphasized repeatedly (33-36). It is stressed here again because much of the confusion regarding the causal relationship between ariboflavinosis and corneal vascularity has been due to the various interpretations of the extent of corneal invasion.

The corneal vascularity of well developed riboflavin deficiency always occurs in the entire circumference of the cornea. This fact is important for correct diagnosis. In view of the fact that riboflavin deficiency is nutritional and present throughout the organism it is to be expected that both eyes show equally the resulting vascularity. This is true in the great majority of cases, but there are exceptions to the rule. Disease or trauma may condition vascularization in one eye, when the degree of riboflavin deficiency may be insufficient to produce signs in the other eye (37).

Invasion of the cornea by blood vessels occurs in several pathologic conditions. In rosacea keratitis it is usually most marked in the upper quadrants of the cornea, but it may extend all around the limbus. This disease is characterized by subepithelial infiltrates which increase in size and progress towards the center of the cornea and the deeper layers of the stroma. Eventually the epithelium over these areas becomes eroded and the ensuing ulcers attract blood vessels which form a vascularization of the fascicular type (38). This clinical picture is different from that of the ariboflavinotic type of corneal vascularity.

There is disagreement in regard to the beneficial effect of riboflavin in rosacea keratitis claimed by Johnson and Eckardt (31, 39), Johnson (40), Conners et al. (41) and Sohr (42). Fish (43) has seen no therapeutic effect at all in her cases, and Wise (44) also refutes the efficacy of riboflavin in this condition. He found that rosacea keratitis may show exacerbations during intense riboflavin administration. The cheilosis of two of his cases was cured by riboflavin while no change was observed in the corneal condition. In more than 20 cases, he did not observe any definite cure by treatment with riboflavin. Similar negative results have been reported by Zondek, Landau and Bromberg (45) and Jirman (52). The possibility of a conditioned deficiency must be taken into consideration. It may be that a coincidental riboflavin deficiency can aggravate rosacea keratitis, in which case some benefit may be derived from riboflavin administration.

Another condition associated with corneal vascularization is phlyctenular or eczematous kerato-conjunctivitis. Here the situation is quite different. This disease is actually nothing but a manifestation of true ariboflavinosis. McKay (46) saw improvement of phlyctenular keratitis under riboflavin treatment and the same observation was made by Cosgrove and Day (47) and Rubino et al. (48). Stern and Landau (49) examined systematically the effect of riboflavin on phlyctenular kerato-conjunctivitis. They found that patients suffering from this condition made a dramatic recovery with riboflavin by mouth, without any local treatment. This is astonishing, as the usual treatment of phlyctenular keratitis with yellow oxide of mercury, atropine, cod-liver oil, etc. is a very tedious affair in many cases. Phlyctenular keratitis is most commonly regarded as an allergic condition. It occurs mainly in undernourished children who show the stigmata of "scrofulous" diathesis. The hypersensibility of the conjunctival and corneal tissues is supposed to be caused by a hidden, perhaps clinically healed, tuberculous lesion, but not necessarily provoked by the tuberculous antigen but also by other bacterial toxins (hetero-allergy).

Clinically there is a striking similarity between phlyctenular keratitis with eczematous pannus and the ocular picture of ariboflavinosis. The corneal vascularization seems to be identical. The cheilosis and the dyssebacia of the naso-labial fold in ariboflavinosis strongly resemble the eczematous lesions of the face in eczematous keratitis. The acute ocular manifestations of ariboflavinosis as described by Mann (35) and Stern (50) are very similar to typical cases of eczematous keratitis.

Eczematous keratitis represents, no doubt, an allergic reaction in many cases. In sensitized men and animals the condition can be produced by instilling a drop of allergen into the conjunctival sac (Calmette's reaction). But it is also known that patients belonging to this group of "scrofulous" individuals frequently have a craving for carbohydrates, which they consume in great quantities—a diet likely to lead to ariboflavinosis.

Stern and Landau found, in fact, that their patients showed very low riboflavin values in the urine. This, together with the therapeutic effect of riboflavin, certainly suggests that eczematous keratitis is a manifestation of ariboflavinosis, released by unspecific stimuli of an allergic nature in predisposed individuals. These unspecific stimuli may be naso-pharyngeal disorders, infectious agents or even mechanical irritation. Ariboflavinosis, however, is always the essential basic condition.

Another disease characterized by corneal vascularization is trachoma. Typical trachomatous pannus is limited to the upper third of the corneal circumference and cannot be confused with ariboflavinotic vascularity. There are cases, however, in which a marked discrepancy exists between the appearance of the cornea and that of the palpebral conjunctiva. The latter may be entirely smooth and well cicatrized and yet a marked pannus may extend over the cornea. The patients complain of watering, itching and burning, and sometimes even exhibit marked photophobia. This condition often proves very difficult to treat.

The most efficient treatment of active pannus in trachoma is that of the diseased palpebral conjunctiva. In the condition to be discussed here, the palpebral conjunctiva is inactive and not amenable to treatment. Unspecific treatment with atropine, etc. alleviates the symptoms, but it is very tedious and does not prevent relapses. Operations like peritomy and peritectomy have been suggested and abandoned because their results are decidedly unsatisfactory. When one examines cases of this kind carefully with the slit lamp, one frequently finds that the cornea is vascularized not only in its upper half or third as in classical trachomatous pannus, but in its entire circumference as in ariboflavinosis (51). Treatment with riboflavin promptly relieves the condition.

The therapeutic success in such "intractable" cases of trachomatous pannus is considered to mean that they are provoked by ariboflavinosis, causing typical vascularization of the cornea. The vessels of the trachomatous pannus never leave the cornea entirely but remain visible through the slit lamp as minute, empty channels. If riboflavin deficiency occurs at this stage of trachoma, the well-known response of the cornea sets in: the limbic plexus becomes flushed and newly formed capillaries encroach upon the cornea. In the upper half of the cornea, where the old channels of the trachomatous pannus are still present, there is no new formation of vessels but the vessels of the pannus become engorged and present the picture of active trachomatous pannus. Adequate provision of riboflavin will then, of course, exert its beneficial effect on the old pannus as well as on the newly formed vessels.

The above are the only known clinical conditions in which corneal vascularity more or less resembling that of riboflavin deficiency is observed. The resemblance is only superficial in the case of rosacea keratitis, except possibly in some instances where there may be coincidental riboflavin deficiency. Simple, trachomatous pannus cannot be confused with ariboflavinotic vascularization because of its pathognomonic localization, the exacerbations described are due to true ariboflavinosis. Eczematous keratitis is merely a clinical variation of ariboflavinosis.

Corneal vascularity of the same type as in ariboflavinosis has been found to occur in rats on diets deficient in protein or in any one of the essential amino acids. Nothing much is known as yet of the pathogenesis of this vascularization. It is probably due to some metabolic upset in the corneal cells caused by the absence of these substances. A similar type of vascularization occurs in zinc deficiency (53), sodium deficiency (54, 55) and thallium poisoning (56). Although this vascularity is of the same type as that in ariboflavinosis, clinically it generally need not be considered in the differential diagnosis as it seems to occur only under experimental conditions unlikely to be encountered in clinical practice.

It is necessary to discuss critically the statement of a number of workers that corneal vascularity is not an unequivocal sign of ariboflavinosis. Stannus (27), in expressing this opinion, quotes several authors. In checking the original papers one finds that in some instances Stannus' interpretations of the authors' remarks are open to criticism. In other cases it seems likely that Stannus read into the papers a meaning which the authors never wished to express. Stern (37) has pointed out that not one of the papers mentioned by Stannus gives convincing proof of the non-specificity of corneal vascularization.

In some of them the experimental set-up was inadequate (57, 58). In others, circumcorneal injection and other non-specific signs were either accepted as specific (59-63), or the method of examination is subject to criticism. In some instances only one or two sectors of the cornea were examined and not the whole circumference (64). In others, the slit lamp was not used and "grossly visible corneal vascularity" was noted as a sign of ariboflavinosis (65). Finally, a number of the investigators quoted by Stannus actually agree on the specificity of corneal vascularization in ariboflavinosis (66-69, 33, 34). In the case of thallium poisoning, mentioned above, Stannus even misquotes the original paper and speaks of thallium deficiency.

McCreary, Nicholls and Tisdall (70) make an important point which, however, does not disprove our thesis of the specificity of corneal vascularity. They found that the corneal vessels of ariboflavinosis never disappear entirely but rather become invisible when they are anemic and collapsed following relief of the deficiency. They can refill at any time in response to non-specific irritation. This observation corresponds with that in trachomatous pannus, where the vessels persist as empty channels all through the life of a patient. This fact appears to be a possible source of error. Even if it is agreed that corneal vascularity of the type discussed is always originally due to riboflavin deficiency, a flare-up at a later stage may be caused by a non-specific reaction to any kind of irritation. In such instances no response can be expected to riboflavin therapy.

In the foregoing an attempt has been made to arrive at an answer to the question of the specificity of corneal vascularization as a sign of ariboflavinosis. We believe that vascularity of the type described is in fact a pathognomonic sign of riboflavin deficiency. Another question arising in this connection is whether ariboflavinosis always causes corneal vascularization.

Williams et al. (71) found no corneal vascularity in 4 subjects maintained for 9 months on about 0.8-0.9 mgm. of riboflavin per day. However, neither this amount nor about 1.1 mgm. per day prevented a certain depletion of tissue riboflavin as measured by load tests. Keys et al. (72) observed no corneal vascularization in their test subjects who for nearly 6 months were supplied with only about 0.9 mgm. of riboflavin daily, and Davis et al (73) found that 0.6-0.7 mgm. per day failed to cause corneal vascularity (It must be noted that Davis and her associates did not use a slit lamp for their investigations). About 1.3 mgm. per day were required to prevent tissue depletion as assessed by load tests. Sebrell, Butler, Woolley and Isbell (74) found that 0.5 mgm. per 2400 calories for 3-8 months resulted in distinctive physical signs of deficiency, but they did not record any observations on the cornea.

It seems that a low intake of riboflavin must continue for a prolonged period of time before anatomical signs of the deficiency, and particularly corneal vascularity, make their appearance. This is surprising in view of the fact that riboflavin is water-soluble and might be expected to be washed out of the organism in a short time in a deficiency state. It can perhaps be explained by assuming that riboflavin is bound in the organism to the protein of enzymes and cells. How low the tissue concentration of riboflavin has to fall in the cornea before corneal vascularization sets in has been shown experimentally by Bessey and Lowry (26). In rats on a riboflavin deficient diet, the first signs of corneal vascularity appeared only when the riboflavin concentration of the cornea fell to less than 50% of the normal. In rats on a comparatively riboflavin-free diet this stage was reached in 3 weeks, but in animals on a diet containing only slightly less than the optimum it took a considerably longer period of time.

Jolliffe (75) insists that biochemical changes and impairment of function usually precede morphological changes in deficiency conditions. Corneal vascularity is a relatively late result of functional disturbance and is an expression of a well established deficiency. It represents the response of the organism to a degree of impairment of function that makes the continuation of normal metabolic processes impossible.

A deficiency disease may be caused not primarily by an inadequate diet but rather by interference with absorption or utilization of the essential nutrients, or by increased requirements, destruction or excretion. Jolliffe has termed these states "conditioned" malnutrition, and Kruse (81) has recently given this concept an important place in the science of nutrition in a masterly paper on the etiological complex of deficiency states. He brings the ensemble of conditions into proper perspective and shows how conditions other than a poor diet affect the production and character of deficiency disease. I (37) have published reports of cases of corneal vascularity after surgical trauma to the cornea (corneal transplantation), where the trauma is to be regarded as the conditioning factor. The healing process after trauma causes increased activity of the corneal epithelium and stroma with a correspondingly higher oxygen requirement. Thus, a degree of riboflavin deficiency which remains subclinical under normal conditions may lead to corneal vascularization when other pathological conditions cause the corneal metabolism to be on a higher level. Prolonged deprivation of riboflavin, in experimental animals, causes a definite handicap to the healing process of experimental corneal lesions (76).

While examining unselected patients in Palestine, I found a considerably higher prevalence of ariboflavinotic corneal vascularity among them than among the selected malnourished patients of the Lower East Side Nutrition Clinic of the New York City Health Department. I do not believe this to be due to a less satisfactory diet among the patients in Palestine. The very high incidence of seasonal Koch-Weeks conjunctivitis and trachoma in Palestine probably puts an extra strain on the corneal metabolism and represents a conditioning or precipitating factor for the corneal vascularization. The same applies to phlyctenular conjunctivitis as shown by myself and Landau (49). In this case a subclinical riboflavin deficiency is conditioned by an allergic reaction and results in the so-called phlyctenular pannus which is nothing but the typical vascularization of ariboflavinosis. In a case report on a patient who had developed heavy vascularity of the cornea caused by a serious riboflavin deficiency, conditioned by superficial corneal injuries, I (77) arrived at the same conclusion. And finally I (50) observed a patient with maximal vascularity of the cornea in chronic riboflavin deficiency, conditioned by an acute sore throat with high fever which increased the riboflavin requirements of the organism.

This, then, is the answer to the question why every case of dietary riboflavin deficiency does not display signs of corneal vascularity. Unless the deficiency has reached considerable proportions, or unless a conditioning factor comes into play, corneal vascularity will fail to appear.

Treatment

It seems obvious that a deficiency ought to be cured by the administration of sufficiently large doses of the lacking element. Even higher doses than required physiologically might be administered therapeutically, although the rationale of this overfeeding of the organism is not quite clear, particularly in the case of riboflavin. The recommended dietary allowance of the human organism is about 1.5-2.5 mgm. per day (more during pregnancy and lactation). Riboflavin is not accumulated in the organism to the same extent as are the fat-soluble vitamins, no major depots are available in a deficiency state, and the supply of the normal demand should be sufficient to establish a well-balanced function. Empirically it has been found, however, that it is advisable to give therapeutically at least 5-10 times the amount required physiologically. This points to a possible explanation of therapeutic disappointments. If the five to tenfold amount of the vitamin is necessary to cure a deficiency state, it seems likely that the real cause for them is not a lack of intake but a faulty utilization of the amount offered in the normal diet. Should this be true, then even a sufficient supply of dietary riboflavin would not saturate the organism. Faulty absorption of riboflavin in the gastro-intestinal tract owing to disorders in this system is another possible explanation of riboflavin deficiency appearing under a well-balanced dietary regimen, and a reason for higher therapeutic requirements.

It has been pointed out previously that riboflavin occurs in nature together with all the other B complex factors and that a deficiency of riboflavin alone should really not be supposed to be possible. What happens is probably that a general deficiency of the vitamin B complex remains subliminal and that the first clinical sign to appear is the one due to a lack of riboflavin when the condition reaches pathogenic proportions. Vascularity of the cornea can therefore be cured clinically with riboflavin alone; it is, however, safe to assume that the other B factors are also lacking to a certain degree and it would seem advisable to treat these cases not with riboflavin alone but with the whole vitamin B complex. Therapy with riboflavin alone is theoretically interesting but biologically satisfactory results can be obtained only if the complete B complex is given. It is more important still to realize that vitamin therapy is at its best a substitution therapy. The cause for the deficiency has to be found, be it dietary or organic, and eliminated at its source. It is probable that the greatest importance of vitamin deficiency in clinical medicine lies in border-line cases of ill-health which frequently puzzle the physician and disable the patient. It is quite possible that in partial avitaminosis the cumulative damage to the important epithelial structures of the eye may lower their vitality, favor the incidence and prolong the activity of infection and precipitate degenerative changes on a wider scale than is yet realized (78).

Acute Manifestations

In the preceding section the ocular signs of ariboflavinosis were described as they occur in cases taking a more or less chronic course. This is not always the case. The condition can assume the aspect of a violent, acute disease (35, 50). Such cases present a very marked photophobia and intense hyperemia, mainly of the bulbar conjunctiva. No mucous or purulent discharge is present but lacrimation is profuse. The conjunctival smear is sterile or shows harmless saprophytes. With the slit lamp the limbic plexus is seen to be maximally engorged. The loops, transformed into tiny convolutions of capillaries, send out fine vessels three, four or more millimetres into the subepithelial corneal layers. These newly formed capillaries sometimes stand out plastically from the corneal epithelium. The epithelium covering the vascularized part of the cornea is edematous and shows cyst-like vesicles filled with clear fluid. They may break down and produce small ulcers that stain with fluorescein.

Gross dietary deficiency frequently can be found and, in some cases, the condition is provoked by acute infections such as tonsillitis. Mild signs of other deficiencies of the vitamin B complex frequently can be observed, such as pellagroid pigmentation of the skin and over-active tendon reflexes. I believe that these cases represent acute exacerbations of long-standing chronic deficiency states, provoked by a sudden deterioration of the general state of health. Acute infectious diseases, gastro-intestinal disorders or similar occurences probably will always be found in the anamnesis.

The condition looks alarming so that hesitation may be felt about limiting therapy to riboflavin. The prompt response of the eyes to this medication is, however, most gratifying and local treatment generally is superfluous.

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AMINO ACID DEFICIENCY

Etiology

T. T. Chang and his associates seem to have been the first to observe corneal vascularization in tryptophane deficiency (1). One year later, Totter and Day (2) made the same observation; rats on a tryptophane-deficient diet, who received sufficient amounts of vitamin B complex, developed vascularity of the cornea. Totter and Day described it as being different from that seen in riboflavin deficiency, vascularization beginning opposite the outer canthus and not in the entire periphery. This difference has not been noted by subsequent workers, but the occurrence of vascularization has been confirmed universally (3-7). Most of the other essential amino acids produce the same effect when absent from the diet of experimental animals: leucine (7, 8), histidine (7, 9), lysine (10), methionine (11, 12), isoleucine (7), threonine, valine, arginine and phenylalanine (7, 13).

Pathology

Sydenstricker and his group have made careful histological studies of this type of corneal vascularization (12, 13). The first sign of ocular reaction to any of these deficiencies is a congestion of the scleral conjunctiva and engorgement of the limbic plexus. This is followed by slight thickening and diffuse corneal clouding; capillary "sprouts" shoot from the marginal limbic vessels. Distal to the end of new capillaries, an increased number of cells can be observed; they are similar to corneal "corpuscles" of the phagocytic type, but vary somewhat in size and shape. Later on, a larger and longer type appear which are identical with the endothelial cells seen in the capillary walls. These morphological findings seem to point to the possibility that the endothelial cells actually derive from corneal cells.

This corneal vascularity seems to resemble closely that observed in riboflavin deficiency; however, deep vascularization seems to be not uncommon and keratinization of the epithelium also frequently distinguishes it from ariboflavinotic vascularity (8, 9). Keratinization of corneal epithelium was observed in rats on diets deficient in leucine and histidine, and in a very pronounced degree in valine deficiency (8, 9). Ferraro and Roizin coined the name "nutritional corneal dystrophy" for this condition. It is reversible if treated in time with the missing substance. It is important to note that it does not respond to riboflavin administration but does respond promptly to supplementation of the diet with the missing amino acid. Amino acid deficiency must, therefore, exert some direct effect upon the cornea rather than act by inducing a deficiency of riboflavin, as was suspected at one time (14).

Very little is known about the pathogenetic mechanism of corneal vascularity in amino acid deficiency. Follis (15) has pointed out that the relationship of tryptophane to nicotinic acid synthesis has assumed great importance and the possibility that pellagra may be in part the result of tryptophane deficiency, inasmuch as cornmeal contains so little of this amino acid, appears to be a real one. It seems to be the consensus of pellagra workers that the occasional corneal vascularity in pellagra is due to a concomitant riboflavin deficiency. However, there seem to be interrelationships of the utmost importance and relevant information can be expected to result from investigations concerning these relationships.

If animals maintained on a tryptophane deficient diet receive this amino acid in pure form apart from their regular meals and at certain intervals from them, corneal vascularization sets in, in spite of the feeding of tryptophane. This means that tryptophane must be ingested together with the other nutrients to be effective (16).

Prevalence

In rats, general protein deficiency, not only deficiency of a single amino acid, may result in the appearance of corneal vessels. In man, however, this has never been observed (11). A clearcut deficiency of a single amino acid is unlikely to occur clinically in man, and it is doubtful whether it ought to be taken into consideration in the differential diagnosis of corneal vascularity. This chapter is, however, far from being closed. Givner (19) has observed two cases of exfoliative dermatitis with corneal changes similar to those seen in experimental valine deficiency. Administration of amino acids parenterally and aminoids and protein by mouth was followed by clearing of the cornea and resulted finally in complete recovery.

A tryptophane deficient diet has been administered for short periods to human volunteers by Holt and coworkers (17) without the appearance of any significant ocular changes.

Amino acids have been applied externally to one experimentally injured cornea of guinea pigs while the other cornea with a similar injury was treated with isotonic saline as control. Regeneration of the cornea in the eye treated with amino acids was much more rapid (18).

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KERATOCONUS

The etiology of keratoconus is far from clear. Heredity seems to play a role, endocrine multiglandular disturbances have been suspected, and Demole and Knapp (1) showed that a lack of vitamin E in the diet of rats occasionally led to keratoconus and other ocular disturbances which could be cured by administration of the missing factor. Mandach (2) treated successfully a case of acute keratoconus in a 12 year old girl with vitamin E, but other cases of stationary keratoconus did not benefit. Carreras (3) treated keratoconus in a 26 year old male with daily injections of 30 mgm. of vitamin E (alpha-tocopherol) to a total of 240 mgm. The irregularities of the Javal images and visual acuity improved in both eyes. The author concludes that the so-called hereditary cases of keratoconus may be produced by a relative deficiency of vitamin E during pregnancy. A post-natally acquired deficit as well as the inborn deficit is accompanied by dysfunction of the anterior part of the hypophysis, sometimes also of other endocrine glands. This, Carreras claims, is the explanation why even in the presence of glandular disturbances the keratoconus can only be influenced therapeutically by vitamin E and not by the products of internal secretion. Early prophylactic treatment with vitamin E promises to be more helpful than treatment of advanced symptoms.

Keratoconus is regarded by Knapp (4) as due to a process of softening of the cornea, similar to that in the sclera presumed by him to be the cause of progressive myopia, and ascribed by him to a calcium and vitamin D deficiency (see p. 51). He observed 11 patients (18 eyes) who received between 14,000 and 45,000 units of vitamin D and calcium salts, the latter varied according to the subject's milk intake (the less milk the patient drank habitually the more calcium was given orally). Knapp reports subjective and objective improvement in his cases which he was able to visualize by comparing plaster casts of the eyes. Knapp's ideas have never been confirmed. The pathogenesis of keratoconus must certainly be assumed to be more complex than that envisaged by him.

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INTERSTITIAL KERATITIS

Vitamin E was reported to be beneficial by Stone (1) in syphilitic interstitial keratitis. Ten patients with this condition, who had all received anti-syphilitic therapy in the past, showed considerable improvement with vitamin E, which could be enhanced by the addition of riboflavin. Vitamin E seemed to be effective mainly in hastening absorption of superficial and deep corneal exudates, thus preventing and reducing scar formation, while riboflavin is thought to have had some effect on the corneal vascularity. Even in long-standing involvement with extensive opacities and corneal scarring, gradual and continuous absorption of opacities was observed with vitamin E therapy, irrespective of the amount of anti-syphilitic treatment received. Stone thinks that this effect of vitamin E is non-specific, but he suspects a nutritional deficiency because some of his patients were in a very poor state of nutrition.

Unfortunately no further work on this matter seems to have been published although the results claimed by Stone would seem to justify systematic investigations on a larger scale.

Attempts to influence corneal diseases not regarded to be due to ariboflavinosis with riboflavin were made early in the short history of this vitamin. The first authors to do this were Kruse, Sydenstricker, Sebrell and Cleckley (2) who observed marked improvement in two patients with severe interstitial keratitis associated with syphilis, while under therapy with riboflavin. It may be, however, that these cases were not suffering at all from syphilitic parenchymatous keratitis but from ariboflavinosis. The authors admit this possibility. Further, they suggest that, although syphilitic keratitis may not be due primarily or solely to a deficiency of riboflavin, such a deficiency might release the pathogenetic mechanism of parenchymatous keratitis.

Their results have been rejected by Johnson and Eckardt (3) who had no success at all in the treatment or prevention of interstitial keratitis with riboflavin. Johnson and Eckardt express doubt whether Kruse and his co-workers had really been treating syphilitic keratitis and not rather a deficiency disease, or else rosacea keratitis, which they found to respond excellently to riboflavin medication (a claim which has been rejected in turn by others, see p. 27). On the other hand, the results of Kruse and Sydenstricker (2,4) have been confirmed by Cosgrove and Day (5) and Corner (6). No definite judgment can be given at present concerning the opposing claims in this matter. It ought to be pointed out, however, that the positive reports on the results of riboflavin therapy in syphilitic keratitis may concern cases of conditioned riboflavin deficiency, which could explain the discrepancy of opinions.

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SPRING CATARRH

In 1944, Castellanos (1) published a paper on his experiences with riboflavin in the treatment of spring catarrh (vernal conjunctivitis). He found that 92% of 105 patients improved within a short time when 1-3 mgm. of riboflavin were given daily by mouth. During this treatment the patients also received eye drops containing adrenalin. He explained this favorable effect by assuming that riboflavin is rapidly destroyed in summer by the increased ultra-violet radiation and concluded that spring catarrh is actually a riboflavin deficiency. Lehrfeld (2) attacked this paper vigorously, denying that riboflavin can conceivably be of any use in the treatment of spring catarrh because the disease has been proven to be of allergic origin. He credited the improvement observed by Castellanos solely to the local treatment with adrenalin.

Gutmann (3) reported the results of vitamin therapy in cases of "Allergic Warm Season Conjunctivitis", his name for vernal conjunctivitis. He observed "remarkable results" in some cases which, unfortunately, are not described clinically. He did not attempt to explain this good effect of riboflavin.

Stern (4) examined the question systematically and found that the palpebral form of spring catarrh with papillary hypertrophy ("cobble-stones") responded favorably to riboflavin by mouth without local treatment. The disease was not cured but the subjective complaints were alleviated and the anatomical changes of the conjunctiva receded somewhat. The palpebral form with milky edema but without "cobble-stone" formations did not respond, nor did the mixed or purely bulbar forms receive any benefit from this treatment. The same results were, incidentally, observed with niacinamide.

Stern associates these effects with the anti-histamine properties which have been ascribed to riboflavin (5, 6), histamine being the pathogenetic agent in this disease which undoubtedly is an allergic condition. The forms of spring catarrh not responding to this therapy are possibly caused by other agents (acetylcholine) known also to be released in certain allergic reactions.

Calcium ion is a therapeutic agent which has been used widely in the treatment of spring catarrh. It is believed to exert a sealing action on the conjunctival capillaries and a certain degree of deficiency of this substance has been suspected. Knapp (7) added vitamin D to this treatment with calcium and reported considerable improvement within one to two weeks in all but one of his 43 cases. All forms, palpebral, bulbar and mixed, received benefit, and the author believes that he has shown a disturbance of vitamin D—calcium—phosphorus metabolism to be of basic importance in the pathology of spring catarrh.

Finally, vitamin C has been recommended in the treatment of spring catarrh by Brecher (8), and thiamine by Bietti (9).

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SJÖGREN'S SYNDROME

Between the years 1935 and 1940, H. Sjögren (1) studied and described a peculiar syndrome occurring with keratoconjunctivitis sicca. In addition to the ocular irritation caused by considerable reduction of the tear production, a defect in the secretion of the salivary and sweat glands results in dysphagia, owing to the dryness of the upper alimentary tract, and dry skin, and there always is present a chronic progressive poly-arthritis. Furthermore, achylia, rhagades at the corners of the mouth and swelling of the parotid glands may be observed. The syndrome, which is now called Sjögren's syndrome, occurs almost exclusively in women after the menopause and is widely regarded as due to endocrine disturbances. However, the fact that avitaminosis A is known to cause degenerative changes in the lacrimal glands (2, 3) and epithelial changes in the conjunctiva and skin suggests a possible relationship. In opposition to this idea are reports that the blood level of vitamin A in patients with Sjögren's syndrome is normal (4, 5) and that vitamin A has no influence on the condition (6). On the other hand, large doses of vitamin A have been reported to exert a beneficial effect (7, 8) and some authors have seen good results with vitamin B complex therapy (1, 5, 9, 10).

Gottfredsen (11) recently has reported a study designed to throw some light on the obscure etiology of Sjögren's syndrome. The disease has several signs and symptoms in common with the Plummer-Vinson syndrome (dysphagia sideropenica) and ariboflavinosis. He investigated 23 women suffering from Sjögren's syndrome and found that the Plummer-Vinson syndrome actually formed part of the pathological picture in three cases. In spite of numerous clinical features common to all three conditions, Sjögren's syndrome differs essentially from ariboflavinosis and Plummer-Vinson's syndrome. The poor effect of therapy with iron and riboflavin is proof of that.

It does not seem likely that a deficiency of iron, riboflavin or vitamin A will prove to be the etiological factor, but this is as much as can be said at present. No effective treatment is known as yet, and cauterization of the puncta lacrimalia and the instillation of liquid paraffin and similar bland drops seem to be the only remedies generally recommended for the ocular signs.

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MYOPIA

Investigations of the importance of vitamin D and calcium in ocular pathology have been almost entirely the monopoly of one writer, A. A. Knapp. His therapeutic attempts with these substances in keratoconus and spring catarrh have been mentioned before (pp. 45 and 49). The high calcium content of the sclera and the low calcium level in the blood of patients with progressive myopia induced him to accept the view that myopia represents "scleral rickets". According to him, the presence of a calcium inbalance together with a vitamin D deficiency may cause a weakening of the fibrous tunic of the eye and give rise to myopia. In experiments on dogs he showed eye signs similar to those commonly found in human myopia: prominence of the eyes, wide palpebral fis-

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sures, ectasia of the cornea and deep anterior chamber (1). Histologically the sclera of the animals showed edema and an irregularity in the arrangement of the fibers. Knapp thinks that the assumption of vitamin D deficiency as a causal factor in myopia explains the rarity of myopia in the rural population, in American Indians and in persons living in high altitudes, these groups being exposed to intense ultra-violet irradiation, and its frequency in the Chinese. Knapp selected 53 patients of 3 to 20 years of age with progressive myopia and treated them with calcium and vitamin D. In 16 of them he found a reduction of the myopia and 7 remained stationary after having been treated for 5-28 months. In several cases he could take plaster casts of the anterior segment of the eyes and demonstrate an actual shrinkage of the eyeball. In a later paper (2) Knapp reported similar results and claims to have also observed an improvement of the hemeralopia accompanying myopia. This latter statement is particularly irritating because massive doses of vitamin D have been reported elsewhere (3, 4) to be directly antagonistic to vitamin A and to facilitate the appearance of vitamin A deficiency signs like keratomalacia in rats.

Knapp's results have never been confirmed. They have been rejected emphatically—and convincingly—by Laval (5) who refuses to admit any association of the genesis of myopia with calcium and vitamin D.

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VITAMIN TREATMENT OF A VARIETY OF CORNEAL DISEASES

Riboflavin

Certain corneal conditions have been reported occasionally to be favorably influenced by riboflavin: superficial punctate keratitis (1), corneal ulcer (1-3) and catarrhal infiltrates (3). In considering these reports the question arises whether it is admissible to assume an unspecific pharmacodynamic effect of riboflavin on a multitude of corneal diseases. It is certainly not likely that they are all primarily due to riboflavin deficiency. Pirie (4) pointed out that riboflavin fulfills a special function in the cell, and that it can only be of use when this specific function is upset. It is useless to hope that riboflavin will help in conditions where the disturbance is due to other causes. While this reasoning is doubtless correct, it seems that not enough is known about the respiratory processes of the cornea which, owing to the absence of hemin substances, are quite different from those of structures provided with a vascular network. Why should it not be possible for bacterial or allergic toxins to have an unfavorable influence on this subtle process? It is quite imaginable that a copious supply of riboflavin will either provide the cornea with an extra amount of respiratory enzymes vital in a pathological upset, or else replace those enzymes which might have been used up in the process of overcoming the pathological condition. Moreover, there are quite a number of corneal diseases the etiology of which is far from known and which may, sooner or later, reveal themselves as due to a disturbance of riboflavin metabolism. Phlyctenular keratitis is an example.

Thiamine

Short mention may be made here of the favorable results claimed for thiamine therapy of herpetic infections of the eye. Nitzulescu and Triandaf (5) observed rapid improvement in herpetic keratitis with thiamine injections which ameliorated the pain and seemed to stop the progress of the local lesion. Grandi (6) had similar results in disciform keratitis, and Cantuliera (7) in this condition and punctate keratitis. Gross (8), finally, recommends local injection of thiamine in glycerine for ophthalmic herpes.

Vitamin C

Uchida (9) observed that the cornea of rabbits has a selective absorptive power for vitamin C, and that vitamin C penetrates into the aqueous through the healthy cornea. It is known now that corneal respiration is mediated by another vitamin, riboflavin, but it was suggested in 1940 by Livingston and Walker (10) that vitamin C might be of value in preventing or counteracting the peculiar chemical and physical effect of mustard gas on the cornea; vitamin C, being a redox substance, was thought by the authors to prevent the interaction between mustard gas and the corneal tissue. This conception was, however, invalidated by Mann and Pullinger (11) who showed in animal experiments that the intravenous administration of vitamin C neither prevented nor influenced the progress of mustard gas lesions of the lids, the conjunctiva or the cornea.

Keith Lyle and McLean (12), on the other hand, obtained striking improvement with vitamin C by mouth in cases of corneal inflammation like superficial keratitis, chronic infiltrates and ulcers in spite of the absence of a vitamin C deficiency. It is true that they simultaneously gave the usual therapy, but it is quite possible that the redox properties of vitamin C had a supportive curative effect. Similarly Summers (13) reported that the addition of vitamin C to the routine penicillin treatment of hypopyon ulcers made the hypopyon disappear more rapidly. That vitamin C may be somehow of importance for the cornea is suggested in the light of Maestro's (14) observations of an increase of vitamin C in the cornea of rats suffering from keratomalacia due to vitamin A deficiency, and of Wolbach's (15) finding that vitamin C is necessary for the formation of collagen in the cornea.

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Chapter II

LENS AND AQUEOUS

VITAMIN C IN OCULAR BIOLOGY

Presence of Vitamin C in Lens and Aqueous Humor

The crystalline lens occupies a unique place in physiology. Devoid of nerves and with no vascular supply, it is freely suspended in the aqueous humor on which it depends for its nutrition. It represents an isolated metabolic system, the respiratory processes of which are mediated by a system of relatively simple chemical compounds which are able to transport hydrogen and oxygen and thus maintain oxidation and reduction activities. They have been called redox substances. Sulfhydryl compounds like glutathione and cystine are known to play a role in these processes. In 1932, Müller (1) reported that he had found another substance in the lens, responsible for reversible oxidation-reduction processes, which he identified with ascorbic acid. The presence of this substance in the lens and the aqueous humor was confirmed promptly by others, and quantitative analysis brought out the surprising fact that the amount of ascorbic acid in the lens and the aqueous was considerably higher than in any other part of the organism, except the adrenals, the sex glands and the hypophysis. Although figures differed with different methods employed and different animals examined, the fact has remained unchallenged that the lens and the aqueous contain ten, twenty or more times as much ascorbic acid as the blood and most other body tissues (2-21).

As mentioned, the figures of many authors fail to agree completely as different methods of estimation were used. The titration method with dichlorophenolindophenol, which is decolorized by reducing agents like ascorbic acid, usually resulted in somewhat higher figures than the biological method which uses the antiscorbutic effect of the substance on guinea pigs kept on a vitamin C free diet (9, 10, 22-24). Fujita and co-workers (25), using Folin's tungstate reagent, stated that only 79% of the reducing effect of lens matter on indophenol is due to vitamin C. A similar result was reported by Johnson (26), who used a spectrographic method for the estimation of vitamin C in the lens. This discrepancy was eventually reconciled by Demole and Müller (27) who showed that the lower values obtained with the biological method were the result of an oxidative destruction of vitamin C. With fresh material, satisfactory correspondence could be shown. Rosner and Bellows (28) finally stated that at pH 2 the total reducing activity of the lens and the aqueous on indophenol is due to ascorbic acid.

The Function of Vitamin C in the Eye

The function of vitamin C in the crystalline lens and its surrounding fluid, together with glutathione and cystine, seems to be the mediation of the oxygen uptake of the lens. This has never been unequivocally demonstrated but can be accepted as an excellent working hypothesis. Presumably, hydrogen from the metabolite is passed along from beta-crystalline to glutathione, to ascorbic acid, which in turn presents it to oxygen for the ultimate oxidation (29). According to Oppenheimer (30), all oxidation catalysts work optimally only at a potential very near to that of the system to be catalyzed. The intermediary catalysts of the lens (ascorbic acid, glutathione and cystine) have probably the task of bringing the potential of the oxidation substrate successively nearer to the last oxygen donator (e. g. fermenthemin in the organism).

Source of Vitamin C in the Eye

As soon as it was realized that the aqueous and the lens contained a relatively high amount of vitamin C, speculation and experimentation set in to find out where it came from. Two possibilities presented themselves at first sight: either it was brought into the eye by the blood and accumulated by the lens and the aqueous, or it was formed in the lens itself and retained there and in the anterior chamber.

The lens of the ox is capable of synthesizing ascorbic acid. Fischer (31) suggested that a reaction which has been shown to occur in vitro may also occur in the living eye: the conversion of lactose into ascorbic acid by cystine, which is present in the lens in considerable quantities. According to Fischer, the following reaction would take place: 1 mol lactose+2 mol cystine→1 mol ascorbic acid+4 mol cystine.

Müller (32) detected another biochemical process ending in the production of ascorbic acid: he was able to demonstrate an increase in ascorbic acid and of reduced glutathione with an increase in sugar consumption, if he incubated ox lenses for 5 hours at 37°C. in Ringer-Locke solution. He suggested the following equation: dextrose + oxidized glutathione→ascorbic acid + reduced glutathione. This formation of ascorbic acid would probably be combined with a process of phosphorylation, as are indeed many processes of carbohydrate metabolism. When phosphorylation was inhibited by poisoning one half of an ox lens in vitro with monoiodo-acetic acid, both halves being incubated in Ringer-Locke solution at 37°C., the poisoned half formed considerably less ascorbic acid than the other one. Franta (21) observed a rise in the ascorbic acid content of the aqueous after intravenous injection of glucose and concluded that vitamin C can be formed in the lens from glucose.

Müller and Buschke (8) believed that they had added further proof that at least part of the ascorbic acid in the aqueous was synthesized by the lens. They succeeded in demonstrating that the high vitamin C content of the aqueous in man was only maintained when crystalline lens was present and intact. In cataract and aphakia the percentage of ascorbic acid in the aqueous falls to almost the level of the blood. This was confirmed by Bietti (33). A further important contribution to the understanding of the complicated metabolic processes in the anterior chamber was made by Müller and Buschke (34) when they found that the ascorbic acid in the aqueous is present in an oxidized form when the lens is intact, but in a reversibly reduced form in eyes with cataractous lenses. Johnson and Zilva (35) reported the same findings. It was concluded that ascorbic acid is brought into the anterior chamber, where, in the presence of a healthy lens, it becomes converted by dehydrogenation into the oxidized form, thus playing its part in the oxidation-reduction system of the lens, and incidentally accumulating in the aqueous. The same conclusion was arrived at by Monjukowa and Fradkin (36).

That the content of vitamin C of the lens and the aqueous is dependent on the presence of it in the blood has been amply proved. This is particularly true for the guinea pig, monkey, apes and man, which are the only mammals unable to synthesize vitamin C. Administration of vitamin C by mouth or parenterally leads to an increase of this substance in the lens and the aqueous (7, 26, 37, 38). Furthermore, it has been shown (21) that interruption of the circulation of the eye is followed by a decrease of vitamin C in the eye. Administration of phlorizin to rabbits is followed by a fall of the ascorbic acid content of the lens and the aqueous (39). This has been assumed to be caused by a disturbance in the absorption of ascorbic acid from the gastro-intestinal tract; it has been pointed out by Guggenheim (40) that it is conceivable that the mechanism is a lack of available glucose for the synthesis of vitamin C by the lens, due to the renal glycosuria caused by phlorizin.

The processes involved have been investigated by Goldmann and Buschke (41-43). They increased the permeability of the blood-aqueous barrier by sub-conjunctival injections of hypertonic saline or intramuscular injection of theophylline and found that the ascorbic acid content in the aqueous decreased, whereas it returned to normal after the increased permeability ceased. Buschke (44) reported similar results after applying adrenaline and acetylcholine locally to the eye: in the case of adrenaline the increase of ascorbic acid in the aqueous after intravenous injection of the vitamin is prevented, while in the case of acetylcholine the injection of the vitamin is followed by a still higher concentration in the aqueous. Ascorbic acid injected into the blood vessels of one eye is reversibly oxidized and the ascorbic acid content of its aqueous increases.

It follows that the blood-aqueous barrier is usually permeable for reversibly oxidized ascorbic acid in the direction blood→aqueous, while it is impermeable in the opposite direction. The high content of ascorbic acid of the aqueous is therefore, at least partly, caused by the following mechanism: (1) supply of oxidized ascorbic acid from the blood, (2) reduction of ascorbic acid by the lens, (3) retention of the reduced ascorbic acid by the blood-aqueous barrier.

This mechanism depends, of course, on the permeability of the lens capsule for ascorbic acid, which has been demonstrated in both directions by Bakker (45) in excised eyes.

That the iris and its network of blood vessels is an important source of the ascorbic acid in the aqueous has been shown by Nakamura et al (46) who demonstrated that the pars pupillaris iridis has the highest vitamin C content of all parts of the eye, and assumed this to be the source of ascorbic acid for the aqueous.

Finally another mechanism has been postulated by Bonsignore (47) to be responsible for the high concentration of vitamin C in the eye. In eyes which have been irradiated with the visible portion of the spectrum, the reduced ascorbic acid content is increased—and that of oxidized ascorbic acid decreased. This is not the case in eyes which are under the effect of atropine. Thinking of a parasympathetic action, Bonsignore applied parasympathetic stimulators (acetylcholine, pilocarpine, eserine and doryl) locally and found that their action was similar to that of light, i. e. the proportion of oxidized and reduced ascorbic acid in the anterior chamber was changed in favor of the reduced form. Animals which received great amounts of vitamin C but were kept under atropine did not show the normal increase of vitamin C in the aqueous. It was concluded by this author that the high vitamin C content of the aqueous and the lens is due to a stimulation of the iris epithelium by way of the parasympathetic system.

In the foregoing an attempt has been made to give a chronological account of the work on problems concerning vitamin C in the eye. In the past few years, parallel with the growing realization that nutritional deficiency of vitamin C is probably of no clinical significance in ocular pathology, investigations on the physiology of this vitamin in the eye have moved to a different level. The main stress is laid now on the mechanism of the appearance of vitamin C in the aqueous, a question closely related to the highly complex biochemical happenings at the blood-aqueous barrier. Significant progress has been made in this field, but it is not possible for me to follow this new avenue which has left clinical areas altogether and approaches the lofty regions of biochemistry.

In order to round off the picture presented by the newer knowledge of the role of vitamin C in the eye, a short review will suffice. The high concentration of vitamin C in the aqueous, compared with that of the blood, postulates an active process of secretion. Energy for this process is available as a result of a difference in the respiratory enzymes of the epithelium and the stroma of the ciliary body (48). The ciliary processes of cows, and the ciliary body and iris of rabbits and pigs, contain a considerable amount of ascorbic acid, as well as glutathione. These substances are to be regarded as the principal substrates of the respiratory and secretory functions of the ciliary body. A portion of them is normally located in the extracellular interstitial fluid of the ciliary stroma and available as mediator between the stroma cells and the stroma-epithelium barrier in the redox chain regarded as source of the energy of secretion of intra-ocular fluid (49). The role of ascorbic acid in these processes has been ascertained by depleting guinea pigs of ascorbic acid: the oxidation-reduction potential of the ciliary tissues is dependent on the presence of ascorbic acid, which must be regarded as a mediator in the redox processes mentioned. In the absence of ascorbic acid, the ionic electric current generated by the oxidative-reductive interaction between epithelium and stroma can be demonstrated to be considerably reduced by observing the movements of basic dyes in the tissues. The passage of this ionic current is accompanied by the transfer of water, and Friedenwald and Herrmann (48) showed that the ionic current postulated by their theory has the proper direction to carry water from stroma to epithelium. Ascorbic acid plays an important part in this mechanism and, in guinea pigs at least, the presence of ascorbic acid is required in the tissues for its normal operation. The rate of water transfer is reduced if the animal is deprived of this mediating substance. Friedenwald and his associates (49) proceeded to show that ascorbic acid is not excreted directly by the capillaries but stored in the stroma of the ciliary body, where it is reversibly bound to an acidophilic substance, and that it is oxidized during the process of secretion into the anterior chamber through the epithelial barrier.

Indirect proof that ascorbic acid enters the aqueous by a secretory process has been given by Kinsey (50) by showing that, with increasing concentration of ascorbic acid in the blood of rabbits, this substance increases rapidly in the aqueous—up to a certain point. With a serum concentration of 3 mgm. per cent the concentration in the aqueous reached 50 mgm. per cent, but higher serum concentrations failed to cause further increase in the aqueous. This means that the transfer of ascorbic acid occurs as a result of a mechanism limited by some factor other than the quantity available in the blood, in other words a secretory mechanism. It is important to note that this process is active only in adult animals. In young animals the concentration of ascorbic acid in the aqueous follows directly and without limitations the concentration in the blood, the factor determining the distribution ratio, therefore, is diffusion, and not secretion as in adult animals (51). Similar findings were reported (52) for monkey and man; in monkeys the ascorbic acid concentration in the aqueous increases from that in the blood to that characteristic of the adult eye during the period of 6 weeks to 6 months after birth. In the human being a similar rise occurs between the 5th and the 9th fetal month.

It may be said, in summary, that Friedenwald and Buschke seem to have given the most satisfactory theory of the function of ascorbic acid in the eye and the mechanism of its appearance there. According to this theory, ascorbic acid is a mediator in the oxidation-reduction reactions associated with the transfer of electrolytes from the blood to the posterior chamber. During this process it is oxidized, in which form it is normally found in the anterior chamber, and is in turn reduced again by the sulfhydryl groups in the lens. It represents thus an oxygen carrier in the respiratory processes of the lens. The reduced ascorbic acid accumulates in the aqueous because the aqueous-blood barrier is impermeable to it.

Vitamin C plays an important role in the respiratory processes of the lens. In pathological conditions these processes are disturbed, and the vitamin C metabolism reflects this upset. As the lens ages, its respiration becomes less intense, and it can be demonstrated that the lens nucleus contains less vitamin C than the biologically more active cortex (53-56). With increasing age, the respiratory activity of the lens gradually decreases, and it has been found, accordingly, that the vitamin C content of the lens becomes less—an occurrence which is, incidentally, not limited to the lens but can be observed in all body tissues (54, 55, 57-59). If the respiratory processes of the lens are suppressed by cataract or absence of the lens, ascorbic acid is found in the aqueous in the reversibly reduced form alone; it is, in contradistinction to oxidized ascorbic acid, easily reabsorbed into the blood and its concentration in the eye is thus found to be equal to that in the blood.

Cataract

In senile cataract the vitamin C content of the lens and the aqueous drops to almost zero (8, 10, 15, 16, 22, 33, 36, 54, 57, 59, 70). It was, of course of the utmost interest to establish whether this absence of vitamin C in the cataractous lens is a cause or a consequence of the lens alteration.

The problem can be attacked in three ways: either by trying to produce cataractous lens changes experimentally through feeding vitamin C deficient diets to animals; by endeavoring to reverse cataractous lens changes with therapeutic vitamin C administration; or by comparing the vitamin C metabolism of normal subjects with that of patients with cataract.

The last method mentioned failed to give a convincing answer: Bellows (16) reported that 6 subjects with cataract had a lower concentration of vitamin C in the blood than 6 normal subjects of corresponding age (0.605 mgm. per cent per 100 cc. as compared with 1.02 mg. in healthy subjects). Seefried (60, 61), comparing 44 cataract patients with 25 normal persons of similar age groups came to the same conclusion: cataract patients required higher amounts of vitamin C intravenously before they eliminated it in the urine than normal persons, a result which seems to point to a disturbance of the vitamin C metabolism in the whole organism rather than in the lens alone. Bellows' findings were challenged by Hawley and Pearsons (62) who denied that the blood of cataract patients showed a deficiency of vitamin C. They confirmed the decrease of it in the urine, normal persons eliminating up to three times as much as patients with cataract. Bouton (63) and Jeandelize (64) reported the same results. Vogt (65) stated categorically that no difference could be found in the physiologically low vitamin C level of old age in normal and cataractous persons, and Nastri (66) regarded the vitamin C deficiency of cataract patients as identical with that of old subjects generally. Gala and Melka (100) concluded from their study of 165 human eyes that the oscillations they observed in the ascorbic acid content of normal and cataractous eyes are of no etiological significance and probably due to seasonal changes. Rados (67), after examining 200 unselected cases of cataract, and finding a normal saturation level for vitamin C in 135 of them, concluded that there is not sufficient evidence to indicate that vitamin C deficiency contributes to the formation of cataract. He denied that the transparency of the lens is dependent on the vitamin C saturation of the organism, and stated that the low vitamin C level in some patients with cataract is but the natural result of old age. Bellows himself, who in 1936 still admitted the possibility of vitamin C being necessary for the maintenance of lens transparency together with sulfhydryl substances, declared in 1944 in his masterly review of the subject in his book on the lens (29) that experimental evidence is insufficient to support the hypothesis of a chronic vitamin C deficiency being an etiologic factor in cataract, as postulated by Monjukowa and Fradkin (36), Müller (68) and Weinstein (15).

The examination of blood and urine of cataractous and normal persons failed to give the required information. The other ways which were open to tackle the question, unfortunately, did not give a more satisfactory answer.

Can experimental vitamin C deficiency produce cataract? This question was examined intensively by a number of workers. Reiss and Nordmann (69) and Nordmann (12) stated that an absolute deficiency of vitamin C was not sufficient to produce cataract. The same opinion is expressed by Viallefont and Diacono (71) and Smaltino (72), while Hou (73) claims to have established an etiological importance of vitamin C deficiency in the pathogenesis of cataract. Bezssonoff (74) thinks that C avitaminosis might fail to produce cataract in experimental animals because they do not live long enough. Bietti (75) is the only worker describing some sort of lens disturbance in guinea pigs with experimental scurvy: he observed fine capsulary granulations in these animals; but it is questionable whether this is directly caused by the absence of vitamin C or by the very poor general condition of the animals. Bourne (76) has pointed out that the physical and metabolic integrity of the lens is to some extent dependent upon the maintenance of a normal metabolism of the whole organism. General metabolic disturbances may affect the lens by creating deficiency of some substance essential to the lens metabolism, by producing toxic substances etc. Monjukowa and Fradkin (36) claimed to have obtained occasional lens changes in young guinea pigs when their mothers were fed on a scorbutogenic diet, and persistent changes when a paracentesis was performed so that the supplies of vitamin C disappeared from the aqueous. They concluded that clinical occurrence of senile cataract depended upon a disturbance of the aqueous-blood barrier in a general background of vitamin C deficiency, a view also expressed by Müller (68). It must be borne in mind, of course, that congential lens changes in the offspring of animals suffering from scurvy is something quite different from senile cataract. There can be no doubt that the greatest caution must be exerted in deciding the question of vitamin C deficiency and cataract development. Artificial experimental conditions may produce cataract in animals together with, but not necessarily because of, a vitamin C deficiency. It seems, after all, of the utmost importance that cataract has never been mentioned as a complication of either scurvy or of its counterpart in infants, Barlow's disease. It seems likely, in our opinion, that the absence of vitamin C in the aqueous and the lens in cataract is secondary to, and not the cause of, the lens changes.

Another group of workers examined the question of the curative effect of vitamin C on lens opacities. Josephson (77) reported that vitamin C was capable of clearing beginning cataract, particularly experimental dinitrophenol cataract. Pavia (78) advocated "a new medical treatment of senile cataract" by intravenous and intra-ocular injections of vitamin C which, he declared, resulted in the clearing of cataractous opacities. The same results were reported by Finlay (79), Cori (in vitro) (80), Muhlmann et al. (81), who saw improvement in 30 out of 60 unselected cases after 2 years' treatment with intravenous injections of vitamin C, and Silva (82). Jeandelize et al. (64) claimed to have observed improved vision in 67 of 80 eyes with cataractous changes in various stages in subjects who received vitamin C by mouth for 20 or more days. Malling (83) and Urbanek (84) deny any therapeutic effect of vitamin C on lens opacities, an opinion also expressed by Vogt (65) Straub (101) and accepted silently by the great majority of ophthalmologists.

The old question of therapeutic action on cataract is much too difficult to be answered with a few experiments or clinical observations, well controlled as they may seem. Lens opacities can remain static or even recede in any stage of any kind of cataract, vision might improve while the lens remains unchanged or even the opacity progresses—these things are too well known to ophthalmologists to require discussion here. The fact remains that, in spite of a few enthusiastic reports, vitamin C therapy has received as much and as little acclamation from theoretical and practical workers as any of the many other cataract cures.

It is remarkable that diseases like uveitis, glaucoma, retinitis pigmentosa, which are known occasionally to cause secondary cataract, are accompanied by low vitamin C values in the aqueous and the lens prior to visible lens changes (53, 10, 70, 99). Naphthalene poisoning of rabbits causes first a decrease of ascorbic acid in the aqueous and only then cataract (85, 86), but vitamin C administered in large doses, while preventing the fall of ascorbic acid in the anterior chamber (85) does not seem to prevent the appearance of cataract! X-ray and ultra-violet irradiation of the eye, procedures which may cause cataract in the long run, provoke a fall in the vitamin C content of the aqueous (85, 87). Interesting as these observations may be, they cannot be regarded as proof that avitaminosis C is the cause of senile cataract.

If we try to summarize the position we find that (1) ascorbic acid seems to have a physiological function in the respiratory processes of the crystalline lens; (2) as these processes slow down in old age, and more so in the presence of cataract, the vitamin C content of the lens and the aqueous humor decreases; (3) the question whether this decrease of vitamin C in the lens and the aqueous is the cause or the result of the disturbances of the lens metabolism has remained undecided, but it seems likely that the second alternative is the correct one.

Post-Operative Hemorrhage

Vitamin C has been shown to be necessary for the healing of wounds. The work leading to this conclusion was summarized in 1942 by Bourne (88). Vitamin C was tried, therefore, as a preventative of post-operative hemorrhage following cataract extraction with iridectomy. Urbanek and Albrecht (89) saturated patients with vitamin C on the day and subsequent to the day of operation and stated that the tendency to post-operative bleeding after cataract extraction was greatly reduced. De Voe (90), in discussing possible causes of post-operative hyphema, included a low vitamin C level of the plasma (lower than 0.5 mgm. per cent). Mann and Pirie (91), however, treated the question with much circumspection and criticism and came to the conclusion that there is no evidence that the occurrence of hyphema following cataract extraction is influenced by administration of vitamin C.

Various Conditions

The occurrence of hemorrhages into different parts of the eye in scurvy is well known and little need be said about it here. Hemorrhages have been described in the conjunctiva, iris and retina, and in rare cases exophthalmos is seen as a result of hemorrhage into the orbit.

A variety of conditions have been ascribed to avitaminosis C or have been treated with vitamin C. Werdenberg (92) and Frominopoulos (93) recommend vitamin C in the adjuvant treatment of ocular tuberculosis. Frydman (94) saw some beneficial influence of vitamin C on the retinal hemorrhages in two cases of Groenblad-Strandberg syndrome, Ciatola (95) stated that vitamin C had some mitigating effect on anaphylactic ocular disease if it is given during the period of sensitization, and Ladame (96) in an interesting self-observation reported on the excellent results he had observed with vitamin C therapy in combating central scotoma which occurred in himself spontaneously or after exertion. Charpy (97) recommends a peculiar treatment of conjunctivitis, gonorrhea, pyodermia, infected eczema, sore throats, headcolds, sinusitis, etc., with overwhelming doses of vitamin A and C: the first day he gives 1.2 million units of vitamin A by mouth, the following 4 days, 600,000 units vitamin A and 10-16 grammes (sic) vitamin C. Mieses-Reif (98) finally recommends vitamin C in cataract, corneal ulcer, superficial keratitis, "fundus changes" and asthenopic complaints of vague etiology.

In the face of extravagant and uncritical statements like the two last ones, and in the absence of systematic work confirming the more serious claims mentioned above, it is not surprising that vitamin C has not found its place in the armamentarium of the ophthalmologist, and much further work ought to be done in order to arrive at conclusive evidence of its value in ophthalmic therapy.

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Pathology

When Thiel (1) observed that the healthy crystalline lens emits a fluorescent light when irradiated with ultra-violet rays he opened a discussion which has not yet subsided. His observation that fluorescence is gradually lost as cataract develops and disappears entirely in the mature cataractous lens stimulated a new line of research on the causes of cataract. Fischer (2) thought that he was able to associate fluorescence of the lens with the presence of flavins. He reported the presence of lumiflavin, the product of photolysis of riboflavin, in cataractous lenses. In 1935 (3), he further reported that he regarded the fluorescence to be due to the presence of "flavins of the vitamin B complex" and halloxazin, a pro-flavin. Halloxazin was found to be absent in cataractous lenses while lumiflavin was again identified.

Fischer's findings have not been verified by other workers. H. v. Euler (4) failed to confirm the presence of flavins in the lens and denied that fluorescence of the lens was due to flavins. A similar conclusion was drawn by György (5). Rochat (6) found lumichrome, not riboflavin, to be present in the normal but not in the cataractous lens; he used the same fluorometric method as Fischer and concluded that Fischer's results must have been due to faulty technique.

The fluorometric method is much less sensitive and elective than the biological method developed by Small and Strong. The fact that lactobacillus casei requires a certain amount of riboflavin for optimum growth is used in this ingenious method to estimate the riboflavin content of tissue and fluid specimens. Philpot and Pirie (36) used it for testing different parts of the eye of the ox and found only insignificant traces of riboflavin in the lens. They succeeded, it seems, in closing the discussion of the relation of riboflavin to fluorescence of the lens in a conclusive way. The only subsequent paper treating this subject is that by Cristini (8) who stated that both normally transparent and cataractous lenses show fluorescence and that the substances responsible for this are not flavins but are the halloxazin substances mentioned previously by Fischer.

Etiology

While the question of the presence of riboflavin in the lens seems to have been answered—in the negative—the problem of the cataract-producing properties of a riboflavin-poor diet is far from having been solved in a satisfactory manner. We are confronted with a curious situation: riboflavin is practically absent from the normal lens, and can be assumed to play no part in its metabolism; yet its absence from the diet has been stated to cause cataract. Vitamin C, on the other hand has been proved to be present in the normal lens in an extremely high concentration, disappears in cataract: but has never been shown to provoke the appearance of cataract by its absence from the diet! In following the argument critically we might be able to find an explanation and a way out of this confusion.

In 1931 Day, Langston and O'Brien (9) first reported cataract in "uncomplicated experimental vitamin G deficiency" in the rat. Within 60 to 87 days, 94% of the animals developed cataract. These findings were confirmed by this group of workers and others in a number of publications (10 (albino rats), 11 (rats), 12 (albino mice), 13 (chicks), 14 (Norway rats), 15 (albino rats), 16 (rats), 17 (rats), 18 (rats)). As work progressed, pertinent facts came to light which led to modifications of the earlier statements. O'Brien (10) found, for instance, that only young rats developed cataract (after 70-84 days), while older rats survived 89-127 days without the appearance of lens changes. Yudkin (11) confirmed this, but signally failed to produce cataract in dogs.

In considering these papers, one fact is of course of the utmost importance: what was called vitamin G or B_2 in those years was by no means identical with riboflavin. It was the vitamin B_2 complex, the heat-resistant part of the vitamin B complex, in contradistinction to the heat-labile vitamin B_1 which was then the only member of the complex which had been isolated in crystalline form. Not before 1935 were riboflavin and nicotinic acid recognized as individual members of the so-called vitamin B_2 complex (19). The vitamin B_2 or G deficient animals were therefore really on diets more or less deficient of all members of the vitamin B complex except thiamine.

This explains a number of facts that puzzled the early workers. Day et al. (13), for instance, noted that a vitamin B_2-free diet produced cataract in chicks; the lens remained unchanged, however, when casein was substituted for egg albumin in the diet. Casein, as we now know, contains riboflavin. The same observation holds for the finding by Langston et al (14) that cataract could be prevented in rats on a vitamin B_2-free diet by adding dry milk in small quantities to the diet. Day et al. (15) expressed the opinion at that time that the growth-limiting and cataract-producing factors were identical, or that the diets they used were similarly deficient in both. It is likely that the second assumption is the correct one.

The isolation of riboflavin in 1935 had a most significant effect on the results of subsequent investigations of the question under review. Experimental animals got less cataract as ability to devise true riboflavin-free diets increased.

Sen et al. (16) saw cataract in 12% of their animals only. György (5) denied all lenticular changes in animals on a riboflavin-free diet. Jansen (20) arrived at the same conclusion. The work of Harris (19) is of particular significance; he fed rats on a diet free of the entire vitamin B complex, adding only crystalline vitamin B_1. With this diet he observed the prompt and uniform occurrence of pellagra and cataract. When all known factors of the vitamin B complex were fed, with the exception of riboflavin, no cataracts were observed! Harris concluded that alimentary cataract might be caused by the simultaneous absence of riboflavin and nicotinic acid. In the meantime Day and Darby (21) were continuing the studies begun by Day, Langston and O'Brien in 1931. They found an inverse relation to exist between the growth of the rat and the incidence of cataract, when graded amounts of vitamin "G" were given. Of animals gaining less than 10 grams weekly, 63% developed cataract, as contrasted to 14% of those gaining 41-60 grams weekly and none of those gaining over 60 grams. Day, Darby and Langston (22) again found cataracts in young rats on a riboflavin deficient diet.

Richardson (23), Eckardt and Johnson (24), Bessey and Wolbach (25) and Luyken (26) observed cataract in only a very small percentage of their experimental animals. Baum et al. (27) made an interesting observation: they demonstrated that cataract could be produced more consistently when traces of riboflavin were present in the diet than when the diet was entirely free of riboflavin. Ninety per cent of their rats on a Bourquin-Sherman diet, receiving about 0.57 gamma (0.00057 mgm.) riboflavin daily, developed cataract within 9 weeks. Another group, receiving crystalline vitamin supplements with the exception of riboflavin, showed the development of cataracts in only 14% after 10 weeks. In a third group, Crisco was substituted for the butter fat of the original diet, and not a single cataract was seen after 12 weeks. These surprising findings seem to point to another nutritional factor playing a part in the pathogenesis of this type of experimental cataract, or perhaps a faulty balance between the different nutrients.

Treatment

It is not surprising that attempts were made very early to influence cataract therapeutically with riboflavin medication. Dor (28) seems to have been the first to suspect that human cataract might be due to vitamin G deficiency. Yudkin (30) demonstrated that the addition of vitamin G to the diet of G-deficient rats, which had developed cataract, was able to stop cataract development. The same author (11) suggested that congenital cataract might be traced back to the mother's dietary inadequacy, even though she suffered no apparent damage, and stated that cataract in rats cleared after feeding vitamin G at an early stage. In a discussion of this paper by Yudkin, Cosgrove reported that, in a group of 50 cataract patients, 64% had lived on diets poor in vitamin G (B_2). Persons in the same age group on a well-balanced diet had not developed cataract to maturity. Day, on the same occasion, expressed his conviction that cataract in man is frequently due to vitamin G deficiency, and suggested therapeutic trials. It was not until 1938, however, that the first results of such attempts were published. They were uniformly disappointing. Wagner et al. (30) treated 11 patients with 21 cataractous eyes with riboflavin. In 9 eyes no change was observed, in 12 the condition had deteriorated. The same negative results were obtained by Richner (31). Derkac (32) reported some improvement in two patients who had received an amazing mixture of drugs (riboflavin, ascorbic acid, crude liver extract, tonophosphan, sodium thiosulfate, cod liver oil and male sex hormones). One of his cases did not return, but the family said he could "read the paper again". The second "improved" case had to be operated on four months after treatment had started. Vogt (33) selected a number of cases of posterior cortical cataract for a therapeutic trial with riboflavin. He used these cases for his experiments because the cortex is more accessible from the outside than is the nucleus, and because these cases less frequently show spontaneous "improvements" than do nuclear cataracts. His patients received riboflavin for 6 months with absolutely negative results.

It has been shown that the results of different workers in the production of nutritional cataract have been equivocal. Before the isolation of the members of the vitamin B complex, the experimental set-up must be regarded as altogether inadequate and the cataracts produced so consistently by Day, Langston, O'Brien, Cosgrove and others were most surely not due to pure riboflavin deficiency but rather to a complex deficiency (19). Many of the differences in these experiments may be due to the use of different diets, or to the use of different strains of rats or different animal species. Young animals seem to be more liable to develop nutritional cataract than older ones; this fact alone should discourage all attempts to treat senile cataract with riboflavin. Nutritional cataract has been produced more consistently in rodents than in other animals. The opinion has been expressed that in higher animals complete ariboflavinosis will cause death before changes in the lens will be observed.

In conclusion, it appears most unlikely that nutritional cataract in the experimental animal is due to a simple riboflavin deficiency. While cataract may occur in certain animals on a deficient diet, it is probable that the essential disturbance is either a combination of several deficiencies, or a factor as yet unidentified and therefore uncontrolled (34). It is certainly not riboflavin, which has been shown to be practically nonexistent in the lens and to have no therapeutic or preventive effect. Bellows (35) considers the need for riboflavin to maintain a normal lenticular transparency in man as entirely hypothetical, and Pirie (7) rejects outright the idea that riboflavin could be of any conceivable importance in the pathology of the lens.

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CATARACT AND AMINO ACIDS

The essential amino acids, deficiencies of which are known to cause corneal vascularization, seem also to be necessary in the metabolism of the lens. A certain percentage of animals on diets deficient in one of the amino acids develops cataract which can be made to revert by feeding the missing substance, if the changes have not progressed too far. A "white opaqueness of the eye" was observed by Curtis and co-workers in rats fed on a protein-poor diet to which no tryptophane was added (1). Others recognized this as cataract (2, 3) and Buschke (4) showed that tryptophane deficiency cataract occurs only in growing animals. Ferraro and Roizin (5) confirmed the occurrence of cataract in tryptophane deficient rats, but noted that lens opacities were seen more often in more mature animals. Buschke (4) described two types of cataract, an acute one which starts in the posterior cortex and spreads to involve the perinuclear and anterior cortical zones, maturing within 2 or 3 weeks, and a chronic one which is confined to the posterior and anterior cortex. Cortical cataracts were also observed in tryptophane deficient swine (6).

Other ocular changes observed by Ferraro and Roizin (7) were edema and congestion of the eyelids and conjunctiva, catarrhal and mucous secretion, symblepharon and occasionally complete closure of the eyelids. These signs were so impressive that Ferraro and Roizin thought the lenticular opacities might be a secondary result of the inflammatory reaction of the external eye.

Other amino acids observed to cause cataract by their absence from the diet of rats are: phenylalanine, histidine and, less frequently, all the other essential amino acids except arginine (8). These workers describe the development of the lens opacities as starting with general haziness, followed by separation of superficial fibers, widening of the sutures, diffuse and granular opacities in the cortex, granular degeneration of the superficial cortex, appearance of refractile lines separating cortex and nucleus, and dense nuclear opacity of variable extent. They also saw lenticular changes of some degree in general protein deficiency.

Exactly as in the case of corneal vascularity, nothing is known about the pathogenetic mechanism of amino-acid-deficiency cataract. The observations of Schaeffer and Geiger (9) have been mentioned in the discussion of corneal vascularity—rats who received a tryptophane deficient diet, and, in separate feedings, the missing amino acid alone, still developed cataract. The amino acid has to ingested together with the other nutrients in order to be utilized.

The effect of amino acid deficiency on the lens is, as yet, of purely academic interest. The lack of concrete knowledge about the biologic fundaments of cataract genesis, however, gives these facts added importance, and we seem to stand only at the beginning of a very promising avenue of approach.

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CATARACT AND CARBOHYDRATES

The well-known frequency of the appearance of cataract in diabetes mellitus belongs to a chapter outside the scope of this review. This occurrence is not in direct relation to questions pertaining to nutrition, and full information can be obtained from the relevant chapters of all text books.

There exists, however, another disturbance of carbohydrate metabolism in which cataract has been observed, and which must be regarded as related to nutritional problems.

Bruck and Rapoport (1) published in 1945 a very interesting clinical observation of galactosemia causing cataract. Galactosemia is a rare anomaly of carbohydrate metabolism in which the metabolism of galactose is impaired and this sugar accumulates in the blood in excessive amounts. Their case concerned a seven-months-old child with vomiting and diarrhea, an enlarged liver and absent tendon reflexes. It was lethargic and somnolent; an eye examination revealed bilateral nuclear cataracts. The blood showed 200 mgm. per cent sugar, half of which was galactose. The child was fed on a galactose and lactose-free diet and the blood sugar returned to normal. The clinical signs and symptoms improved rapidly, and the cataracts cleared promptly. Re-introduction of milk into the diet produced a relapse.

While this seems to be the first published case of galactose cataract in man, it had been known for some years that the feeding of certain pentoses caused cataract in experimental animals. Mitchell and Dodge (2) described in 1935 the appearance of cataract in rats fed on galactose or lactose, and this has since been amply confirmed (3-15). The percentage of cataract formation seems to vary with different breeds, but it has been established that it occurs regularly if the animals are fed on diets containing 50-70% of lactose or galactose and no other carbohydrates. Intraperitoneal injection of galactose has no effect (10). With galactose, the first peripheral opacities appear about the third day and the cataract becomes mature after some 30 days; lactose cataract appears somewhat later.

Another pentose, xylose, also has been observed to cause cataracts in young rats when fed as 35% of the diet (16). No other sugar seems to have cataractogenic properties and the latter authors pointed out that xylose and galactose are derivatives of d-threose, while the sugars which fail to produce cataract are derivatives of d-erythrose.

Little is know about the mechanism of the production of these cataracts. Galactose is toxic to lens tissue in vitro (17) and causes increased permeability of the lens capsule (18, 19). It has been suggested, therefore, that this may exert an influence either on the ionic equilibrium of the lens (20), or that it might allow an escape of glutathione. (8).

There is some convincing evidence of a competition between glucose, which is easily metabolized by normal tissues, and galactose, which is less readily metabolized. This may indicate that under certain conditions excessive quantities of galactose may interfere seriously with the normal oxidation of glucose. The same applies to xylose owing to its configurational relationship. The primary metabolic fault is probably in the liver which is believed to be the site of conversion of galactose into glucose. Galactosemia consists basically of a decreased rate of conversion of galactose into glucose by the liver, resulting in an accumulation of galactose in the blood, and finally thereby, the appearance of toxic manifestations due to the presence of excessive galactose in the tissues (21).

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Chapter III

RETINA, OPTIC NERVE AND VISUAL ACT

NIGHT BLINDNESS

Signs and Symptoms

One of the first, if not the first, symptom of vitamin A deficiency is night blindness. Unfortunately two diametrically opposed terms—etymologically—are used for this condition, hemeralopia and nyctalopia, but, instead of indulging in a linguistic crusade at this point, I prefer to use the term night blindness which is expressive and unequivocal.

It is necessary to point out that vitamin A deficiency is only one of several causes of night blindness. It occurs in all conditions that prevent the rods, cones, or both from participating to their full capacity in the visual process, conditions wherein retinal disease has resulted in destruction or dysfunction of the nervous elements. The adaptation curve will become abnormal according to the kind of elements most affected—rods or cones—and the degree of the impairment. The rods are, of course, the elements responsible for light discrimination in reduced illumination, and, while the function of the cones is also affected in vitamin A deficiency (1), it has been established that for practical purposes the best single criterion is the final rod threshold (1a, 61, 62, 41). Deterioration of dark adaptation is also accompanied by changes in the color sensitivity of the retina. The fields for red and blue may become diminished or even inverted, and a shrinking of the field for yellow may be observed (2). Concentric contraction of the visual fields may occur (18a), a sign probably indicating involvement of the cones as well as of the rods.

Etiology

In starting the discussion of the role of vitamin A in the visual act, some hesitation is felt about delving too deeply into biochemical and physical questions. The amount of information available is enormous, but it seems that it would be a sound scheme to restrict this chapter to questions of clinical importance and to provide but a sketch of the highly complicated theoretical fundament.

The role of vitamin A in the visual process has been the subject of intense study since Wald (3-5) demonstrated that it is an essential constituent of visual purple. Visual purple is a heavy protein molecule with vitamin A as a prosthetic group (16). This compound, also called rhodopsin, exists in the dark-adapted retina and is transformed by light into visual yellow, which, unlike visual purple, is not a compound but a mixture of a carotenoid substance called retinene and a protein. On steady exposure to light, visual yellow changes into visual white, a mixture of vitamin A and a protein. On standing in the dark, vitamin A disappears and visual purple is reformed. For detailed information on the chemistry of the visual substances Hecht's review (7) should be consulted. Peskin (8) has given valuable data on the physical aspect of the regeneration of visual purple, and Morton (9) on the chemical aspect.

Wald (10) found in the retina of some freshwater fish a visual pigment different from visual purple of seawater fish, which he called porphyropsin. This substance is changed by light to retinene$_2$ and vitamin A$_2$, the latter differing from vitamin A in its wave length of maximal absorption (11). Details of the physical and chemical properties of the vitamin A$_2$

compounds can be found in a paper in Nutrition Reviews (12). Porphyropsin, containing vitamin A_2, can be found in vitamin A deficient rats fed on vitamin A_2 (13); this means that vitamin A_2 can replace vitamin A in the bodily functions of the rat.

The carotenoid complexes, which are precursors of vitamin A or provitamins, have been shown convincingly to be of importance in certain biological functions of both higher and lower plants. Phototropism seems to be governed by these chemical substances (14). Light-growth and phototropic reactions, protoplasmatic streaming and chloroplast migration, all exhibit spectral sensitivity curves which have the form and position of carotenoid spectra. The structures which display these reactions all contain carotenoid pigments. Wald regards these facts as convincing though indirect evidence of a possible universality of the association of carotenoids with visual systems. Photoreception, visual and phototropic, throughout all living organisms, may be founded chemically upon this single group of substances.

The change of visual purple into visual white and its reconversion into visual purple is associated with a loss of vitamin A which must be refurnished from dietary sources.

The reason for a vitamin A deficiency may be twofold: either inadequate intake of the provitamin or the vitamin from vegetable or animal sources, or else a disturbance of the process of synthesis of vitamin A in the human organism due to gastro-intestinal or liver disease. The role of liver disease in the etiology of night blindness is demonstrated by the fact that dark adaptation is frequently disturbed in cirrhosis of the liver, hepatitis etc., (15, 16, 17). There is a significant relationship between other nutritional deficiencies and impaired dark adaptation. In chronic alcoholism, where a lack of certain factors belonging to the vitamin B complex is common, fatty changes in the liver and impaired function of this organ can be observed, leading in turn to disturbances of dark adaptation. This observation may be related to the fact observed by Kimble and Gordon (18) that some subjects with impaired dark adaptation, who failed to benefit from vitamin A administration, recovered when riboflavin was added to the therapy. Sloan (18a) has also published observations indicating that riboflavin, in addition to vitamin A, may be required to effect complete recovery from night blindness. In animal experiments it was shown that the administration of thiamine to the diet of rats on a diet deficient in vitamin A relieved the deficiency symptoms to a certain degree (19). The vitamin B complex may thus play a role in the utilization of vitamin A.

The conversion of the carotenoid retinene into vitamin A is effected by an enzyme system which has recently been isolated by Wald and his associates (56). Retinene is vitamin A aldehyde; vitamin A, a primary alcohol. For the reduction of retinene to vitamin A the retina contains an enzyme—retinene reductase; and a co-enzyme—reduced cozymase. This latter substance has as its central component nicotinamide, the anti-pellagra factor of the vitamin B complex. Wald has therefore uncovered the curious situation that a member of the vitamin B complex is helping to regenerate vitamin A in the rhodopsin cycle.

Wald (57) thinks that it is possible that this action of nicotinamide is reflected in physiological disturbances of vision in pellagra. The disturbance would be very subtle—a speeding up of dark adaptation! It is, in his opinion, very likely that it will not occur clinically, but it should be looked for and some interesting results may perhaps be expected from further investigations in this direction.

Another possible relationship is suggested by reports of a beneficial effect of ascorbic acid on hemeralopia. Gorczycki cured a case of hemeralopia with intravenous injections of vitamin C (58), and Stewart (59) observed improvement of dark adaptation under vitamin C treatment (150 mgm. daily), but neither author discusses the underlying mechanism of their surprising observations. Ferguson (60) was unable to detect changes in dark adaptation in volunteers deprived of vitamin C.

Failure of conversion of carotene into vitamin A has been assumed to explain the occurrence of xerophthalmia in two sucklings suffering from severe hepatic insufficiency (20), and generally disease and old age apparently can diminish the capacity of the organism to transform carotene into vitamin A (21). In these cases carotene may fail while vitamin A cures the symptoms of the deficiency. Age seems to play physiologically a part in dark adaptation, and a progressive deterioration of it has been charted amounting to about 0.12 log units for an increase of 10 years (22).

Considerable difficulty was experienced in the attempt to establish experimentally the period of reduced vitamin A intake required to cause disturbances in the light sense. There are several factors which have to be taken into consideration. The most important one seems to be the storage of vitamin A in the liver. As long as this was disregarded in experiments, the results were unreliable, and the opinions of different investigators differed to a large degree. Many persons respond to an experimental vitamin A deficiency with a prompt rise of the rod threshold, while in others it takes weeks or months before deviations of the normal adaptation curve can be observed (1, 23). The latter response seems to be the more frequent one, and Hecht's early observation that the presence of a dietary avitaminosis A becomes evident after the first day of the absence of vitamin A from the diet has been corrected by himself. However, there still seems to be little agreement on the question. Steffens et al (24) failed to observe any sign of vitamin A deficiency as evidenced by photometrical measurements of the threshold values of the macula or an area in the periphery of the retina after having kept volunteers on a diet containing only 100-300 I.U. of vitamin A per day for 44, 160 and 190 days. They think they can find an explanation of this fact in the vitamin A storage in the liver. Booher et al (25) found impaired dark adaptation after 16,271,29,39 and 214 days in their subjects on an A deficient diet, and established daily requirements for the maintenance of a normal dark adaptation of 25-55 I.U. vitamin A and 43-103 I.U. carotene per kg. bodyweight. Edmund et al (26) found similar values: feeding of over 20 I. U. of vitamin A per kg. of bodyweight per day prevented disturbances of the light sense while less than 10 I.U. daily per kg. bodyweight caused mild disturbances. Wald et al (27) investigated the plasma levels of vitamin A and carotenoids in five subjects who had been kept on a high vitamin A intake for 30 days and then deprived of vitamin for 6 months. Within one week after the deficiency diet had been started, the fecal carotenoids had fallen to about 1% of the previous values. Shortly afterwards, the plasma carotenoid levels also became very low. The vitamin A level in the plasma, however, was maintained at the initial maximal values throughout the entire deficiency period. The visual threshold of three subjects also remained constant and minimal; in two it rose slowly to final values of 0.7—1.1 log units above normal. It was concluded that relatively sedentary subjects who are initially well supplied with vitamin A may undergo as much as 6 months of vitamin A deprivation without developing subjective or objective evidences of vitamin A deficiency. Parallel results were obtained by Brenner and Roberts (28). The blood carotene dropped while vitamin A remained constant in five students kept on a deficiency diet for 31 and 20 weeks. No changes of dark adaptation values, the visual field or the structure of the conjunctiva were observed. Ferguson (64) observed the same rapid drop of the carotenoid content of the plasma in human volunteers deprived of vitamin A. The vitamin A level fell much more slowly, reaching about one-third of the original level of 150 I.U. per 100 ml. of plasma in only some of the subjects, and not before 25 months of deprivation. At this level, dark adaptation was still normal. The same findings are reported once more by the same author as a member of a team which carried out what can probably be regarded as the most thorough and comprehensive depletion program on human volunteers to date (67).

On the other hand, again, experimental restriction of vitamin A has frequently been claimed to result in deterioration of dark adaptation after periods of between 20 and 100 days (29-31), and impaired dark adaptation has frequently been found in population groups with diets deficient in vitamin A (31-33).

The general impression which can be gathered from the literature of the last years is that the development of disturbances of dark adaptation in vitamin A deficiency is governed by the previous dietary history of the individual and the amount of vitamin A stored in the liver. This storage is probably not entirely related to the amount recently ingested but more intimately connected with as yet undefined metabolic capacities which differ among different persons (1).

Theoretic calculations, based on the average vitamin A content of the human liver, and on a daily rate of use of 2000 USP units per day without any intake of vitamin A or carotene, make it likely that it takes 1-2 years before the liver loses its vitamin stores (34, 67). Furthermore, the vitamin A content of the retina may be largely independent of the vitamin A level in the blood: A certain amount of vitamin A persists in the retina even when no hepatic stores are available (35) and when the plasma level has dropped to an extremely low value (36). These facts are probably of fundamental importance in the attempts to reconcile the different findings and opinions regarding the effect of dietary vitamin A depletion and the response of dark adaptation disturbances to treatment with vitamin A.

Another factor does not seem to have been sufficiently considered in this connection. Any condition which increases the metabolic need for vitamin A (some of the known ones are: fever, infection, elevated basal metabolic rate, rapid growth, pregnancy) may cause impairment of dark adaptation in spite of a seemingly adequate daily intake of vitamin A (54, 55). Interference with absorption in the gastro-intestinal tract may have the same effect, and it was mentioned previously that disturbances of liver function also interfere with vitamin A metabolism (37, 38, 39, 39a).

Mention must be made also of the criticism leveled at the different methods used in testing dark adaptation. It would lead us too far off our theme if we tried even to give merely an outline of the principles involved. But the fact must be mentioned that many contradictory results seem to be caused by the use of different apparatus, some of them apparently inadequate. Some papers treating these technical questions are mentioned in the bibliography (40-44, 63).

Pathology

Avitaminosis A of long duration has been claimed to provoke fundus changes analogous to those characterizing retinitis punctata albescens and Wilson's disease, and which disappear on therapy with vitamin A (45). This observation seems to be unique and has not been reported since.

The question has been approached experimentally by Myra L. Johnson (46) who produced vitamin A deficiency in rats and examined the retina histologically. Severe deficiency for only a short time failed to produce any structural changes except edema; deficiency over a long period, however, resulted in degeneration, beginning in the visual cells and progressing through the retina to the inner nuclear layer. The outer segments of rods with slight degenerative changes showed a remarkable degree of repair after only 24 hours of vitamin A therapy, and complete recovery after 21-28 days. When the outer segments of the rods were completely degenerated, they were shown to be capable of regeneration after 10-18 weeks. If the degeneration had progressed to the outer nuclear layer or further, no repair could be observed.

Prevalence

Night blindness caused by vitamin A deficiency is frequent in many countries. It is endemic in Scotland

and Newfoundland, where the fishermen and their families are living on diets lacking in vitamin A; for a long period of time these people have been aware that their night blindness can be cured rapidly by eating the fresh liver of sea gulls and of fish (47). In Russia, night blindness was observed long ago to be a result of the great seven-week Lenten fasts (48).

Severe vitamin A deficiency is certainly rare in Western countries. But it is the opinion of Clausen, for instance (49), that about two-thirds of Americans in the lower income groups are receiving not enough vitamin A to assure normal dark adaptation. This opinion has also been expressed by Pett (43) and Mack and Sanders (60) in the U. S., and by Maitra and Harris (61) and Mutch and Griffith (62) in England. In Britain, it has been shown (33) that of those school children who received two-thirds of a pint of milk a day in school 67% had normal dark adaptation, while only 37% of others receiving only one-third of a pint of milk or less daily showed normal dark adaptation curves. However, in view of the lack of unanimity regarding the effect of vitamin A deficiency on the dark adaptation process, it has been pointed out frequently that estimation of the vitamin A level in the plasma is a more reliable guide to the nutritional status of an individual. Measurements of dark adaptation may be used to assess nutritional levels in respect to vitamin A either by the determination of the effect of vitamin A on dark adaptation, or by the comparison of the values of dark adaptation in various groups. The latter method, while not providing such conclusive evidence as the former, may sometimes provide presumptive evidence of the relative nutritional status in respect to vitamin A, and for technical reasons it may be the only feasible procedure (50).

Differential Diagnosis

The consensus seems to be that, while severe deficiency is rare in Western countries, mild deficiency states due to a mild but chronic under-supply of vitamin A are quite frequent. Nevertheless a word of warning seems to be in place. According to Bietti (51), there can be no doubt that wide physiological variations in the light sense occur; there are individuals with a physiologically low sense of light which cannot be improved with vitamin A, and with a normal level of vitamin A in the plasma. Moreover, psychic factors, age, fatigue, depression or ocular lesions—all play a part. Derangements in the light sense cannot therefore be used as an exclusive test for vitamin A deficiency; chemical estimations of the blood content are necessary. Only when the vitamin A concentration falls below a certain limit is there a measurable deficiency in the sense of light. Subjective night blindness disturbances, however, begin only with a much lower vitamin level.

With normal blood values the light sense is usually good. Of subjects with normal average values of light sense a rather small percentage also responds to vitamin A by improvement. Bietti (51) assumes that these individuals have probably an exceptionally good light sense and happen to suffer from a very slight degree of hypovitaminosis; there is nothing to suggest that hypervitaminosis increases the light sensitivity. This has been claimed again, however, lately by Studnitz (59) who states to have found increased capacity of dark adaptation in healthy volunteers who received up to 250,000 I. U. vitamin A daily. The improvement was proportionate to the dosage given, and normal dark adaptation curves reappeared 2-3 weeks after discontinuation of the vitamin A administration. Studnitz assumes that increased absorption of vitamin A increases the formation of visual purple, and insists that it is essential to give vitamin A in emulsion to assure absorption.

Treatment

It seems that recovery from disturbances of dark adaptation is relatively slow. Short term therapy with high doses of vitamin A has only a slight effect and is followed, at most, by a transitory, incomplete recovery. Complete recovery is a matter of weeks and months. Hecht and Mandelbaum (1) reported that, in experimentally produced night blindness, the administration of 10,000 I. U. of vitamin A resulted in recovery after 6 weeks, and in one case it was still incomplete after 3 months, in spite of an increase in the daily doses to 100,000 I. U. Finally even these slow cases recover. Similar results were reported by McDonald and Adler (53) and Wald et al (27). This slow recovery rate indicates some deep-seated lesion, the development of which may be peculiarly favored by the sudden and acute onset in experimental depletion of vitamin A, the long continuance of a deficiency diet, and also perhaps by the sharp restriction of vitamin A alone (27).

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THE ROLE OF RIBOFLAVIN IN VISION

The experimental work of H. v. Euler and E. Adler (1) proved the presence of a substance in the pigment epithelium of the retina of fish and mammals that showed a green fluorescence and changed into lumiflavin under the influence of light. This property is typical for riboflavin, and the authors concluded that it was this substance which they had found in the retina. They suggested that riboflavin has a special function during twilight, transforming light of short wave length into light of a wave frequency for which the eye has a maximum sensitivity. In a later paper (2), von Euler and his co-workers were able to confirm and amplify these findings by using microscopic fluorescence studies and photometric tests. It is worth mentioning that this fluorescence was found to be present also in the eyes of albino rabbits. In 1938, Adler and von Euler (3) reiterated the opinion that flavin may take part in the visual process by means of its photochemical properties such as fluorescence and light sensitivity, a statement which was also upheld by Lythgoe (4). Heiman (5) finally produced an elaborate theory on the significance of the photodynamic action of riboflavin in the visual act.

These papers were followed by a number of others which tried to fit the postulates to certain clinical observations. Kimble and Gordon (6) reported that the night-vision of several subjects with both impaired dark adaptation, as measured by the biophotometer, and reduced vitamin A levels in the blood was restored to normal when riboflavin was administered, after vitamin A had been found to be ineffective. Pock-Steen (7) observed aknephaskopia (twilight-blindness) in over 100 cases suffering from leiodystonia, pro-sprue and pseudo-sprue. This condition, which is characterized by inability to see well in twilight or insufficient artificial illumination, and which is claimed to be different from night blindness, did not respond to vitamin A. The injection of one milligram of riboflavin improved considerably the vision of 67 out of 109 patients. Other subjects needed more prolonged treatment. In subjects where it was without effect, Pock-Steen assumed that the condition had reached an irreversible stage. Boulanger and Swyngedauw (8) also observed a number of cases of impaired dark adaptation that were resistant to vitamin A medication and responded to riboflavin. Similar observations were made by Pollak (9) who had a case of Plummer-Vinson syndrome with abnormal dark adaptation which responded to riboflavin, and better still to brewer's yeast. This latter observation seems to indicate that other constituents of the vitamin B complex also are important in the visual act under low illumination.

Jeghers (10) suggested that these observations point to riboflavin playing a part in the utilization of vitamin A. A similar opinion was expressed by Morton (11) who advanced a hypothesis linking up flavin and carotenoid functions, vitamin A being concerned in the formation of visual purple by performing the reduction of riboflavin, itself undergoing oxidation to vitamin A aldehyde.

The published observations are few in number, and have not remained unchallenged. According to Pirie (12) it is unlikely that riboflavin takes part in the visual process of mammals; it may do so in fish where its concentration in the retina is about 100 times that in mammals. While some of the information available seems to be quite convincing, it is undeniable that further work is required to clarify the issue.

Finally it should be mentioned that Theorell (13) has put forward a hypothesis linking up riboflavin with color vision. It has been refuted by Le Galley and Harrison (14). In carefully controlled experiments they could observe a certain degree of improvement in color vision of color-blind students with high doses of vitamin A and vitamin B_1, and a further improvement with a combination of both. They found, however, no significant change with riboflavin medication. The question has been taken up again recently by Marchesani and Schober (15). According to these authors, intravenous administration of riboflavin resulted in a slight but statistically significant increase of the visual field for red, blue and yellow, but not for green.

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DIABETIC RETINOPATHY

There is some evidence that nutritional imbalance plays a part in the pathogenesis of diabetic retinopathy. De Brux and co-workers (1) expressed the opinion that improper diet and B complex avitaminosis were in part responsible for the typical retinal involvement with hemorrhages and exudates. A frequent finding in poorly treated diabetes with retinopathy is an abnormal plasma protein level. The total quantity may be slightly reduced or normal, but albumen is found to be reduced and beta-globulin increased (2). While adequate treatment with a high protein diet restores the normal balance between the protein fractions in most cases, the retinal condition responds only in a certain percentage; however, it seems certain that improvement in the retinopathy can be expected only if one succeeds in normalizing the abnormal distribution pattern of the blood proteins (3).

It must be mentioned also that diabetic patients have been found to have levels of carotene and vitamin

A outside the range established for healthy persons (4, 13). Thiamine is considerably reduced in the blood (5) and the gastric juice (6) of diabetics, and it has been stated that this vitamin enhances the effect of small insulin doses, decreases the blood sugar of normal dogs and depresses the blood sugar curve in dogs after glucose intake (7). Thiamine deficiency causes a rise in blood sugar and in the glycogen content of the liver and muscles (8). It diminishes carbohydrate tolerance and it has been claimed that administration of thiamine increases the glucose tolerance of diabetics in about 50% of the cases (9). Finally it has been stated that a subcutaneous injection of 4 mgm. of riboflavin decreases the blood sugar in diabetics by 20-30% (10).

Some of these statements are rather sweeping and need confirmation. There can be no doubt, however, that the severity of experimental diabetes in animals is exaggerated by deficiencies of the vitamin B complex (11) and that diabetics with concomitant vitamin deficiency symptoms respond to vitamin therapy with definite and lasting amelioration of the severity of their diabetes (8). Sevringhaus (12), in discussing these findings, concludes that there are numerous complicating conditions which may occur in diabetic patients and which make it advisable to supplement with vitamins while treating diabetes. It seems likely that diabetic retinopathy may be influenced favorably if these therapeutic hints are kept in mind.

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DISEASES OF THE OPTIC NERVE

Nutritional Amblyopia

During and after World War II, numbers of cases of serious neurological and metabolic disturbances nearly always including ocular changes were seen among prisoners of war and internee camp inmates. The greatest number and the most serious cases were observed in the unfortunate victims of the Japanese, but less severe cases were described also in others. In retrospect these cases are comparable to those observed by a number of workers in the malnourished populations of tropical countries. Although the earlier workers did not have the advantage of being able to base their investigations on our present knowledge of vitamin metabolism, their clinical descriptions coincide more or less with the later observations.

Early Japanese writings on beriberi indicate that retrobulbar neuritis, scotomata and oculomotor palsies have been encountered with varying frequency in oriental beriberi (1, 2, 3). Involvement of the optic nerve with paleness of the nerve head and relative central scotomata have also been described in pellagra (4). Vitamin B complex has a beneficial effect on such cases (5-9).

Retrobulbar neuritis is a not uncommon effect of malnutrition in tropical countries, and vitamin B complex has often been reported as being beneficial in its treatment (10-14). Dahlia Whitbourne (15) and F. D. Carroll (16) had occasion to do a very thorough study on a large number of cases of nutritional retrobulbar neuritis in undernourished children. All of the 74 cases belonged to the colored races, were aged between 8 and 14 and there were twice as many girls as boys among them. All except two lived in urban areas. The main complaint of all children was dimness of vision, and this was often the only complaint. About 10% suffered from partial nerve deafness, only one child from ataxia. Photophobia was occasionally complained of, and sometimes other signs of malnutrition like cheilosis and glossitis were encountered. Vision was reduced to 20/40 to 20/200 or less, owing to central scotomata, color vision was sometimes impaired, and while in early stages no ophthalmoscopic changes were seen, temporal pallor was observed when the condition had been present for a longer period of time. Treatment consisted of administration of cod liver oil and vitamin B complex. Unless the condition had been existing for a prolonged period of time, this treatment resulted in satisfactory recovery to normal or almost normal vision and clearing up of the other clinical signs in 45 patients within 2 to 12 months. The rest responded less favorably or not at all. Carroll concludes that it seems certain that the condition is nutritional in origin. The patients were on diets deficient in many essentials, and it is therefore impossible to be sure which factor produced the loss of vision. It is more than likely that one or, more probably, several factors of the vitamin B complex are responsible. In view of certain facts regarding vitamin A, which will be discussed later, a possible importance of this vitamin in the pathogenesis of this condition must be kept in mind.

The observations of Verma (17) indicate a role for vitamin A: according to this worker, 300-400 cases of progressive loss of vision with pallor of the temporal side of the optic disc are seen annually in the Government Ophthalmic Hospital in Madras, India. He examined 48 cases whose condition had started between 10 months and 7 years previously. Visual acuity ranged from 20/40 to 20/400. The patients were in a poor general state of health, 50% of them had angular stomatitis and glossitis, about 35% had xerosis conjunctivae. Treatment with thiamine, riboflavin and yeast resulted in improvement of the accompanying neurological and ariboflavinosis signs, without influencing the visual acuity. Only vitamin A in the form of shark liver oil had an effect on the visual disturbances.

The more recent observations on visual disturbances in prisoners of war (18-56) have, unfortunately, not contributed materially to our knowledge of their etiology. The condition has been called "camp amblyopia" or "camp eyes", terms which seem to have been widely accepted. It is characterized by a retrobulbar neuritis which, if it lasts any length of time, results in permanent damage to the optic nerve. Particularly the highly sensitive papillo-macular bundle suffers to a marked degree. The result is the appearance of central and paracentral scotomata that considerably reduce visual acuity. All patients with "camp eyes" suffered at some period of their captivity from one or, more frequently, several of the following conditions—and I mention only the more common ones: beriberi, pellagra, scurvy, dysentery, malaria, jaundice, paralysis of the limbs, spastic paraplegia, nerve deafness, etc. Ophthalmoscopic examination often revealed optic neuritis in the early stages, but most cases could only be properly examined after their liberation and at this stage the fundus showed temporal or total pallor of the disc and very frequently a peculiar mottled appearance of the macular region of the retina. Owing to the circumstances it was hardly ever possible to perform more than the simplest clinical investigations while the disease was active, and only in a few instances were therapeutic measures taken during this stage. By the time the patients reached proper medical help the condition had usually reached an irreversible stage. Most authors agree that no results can be expected from therapy once the condition has existed for 6 months.

While the majority of observers accept a serious deficiency of the vitamin B complex as the deciding factor in the development of the condition, additional factors have been mentioned as probably also playing a role; the most important ones are these: protein deficiency (22, 37, 42, 48), a hypothetical toxin from mouldy rice (27, 37), general malnutrition (20, 26). It is quite likely that these factors may have a conditioning effect and permit a primary vitamin B complex deficiency to take its malignant course.

Fischer and Morreess (57) have given some foundation to the opinion expressed by several authors (35, 37) that the strong sunlight of the tropics might be partly responsible. They were struck by the similarity of the fundus aspect in the solar retinopathy frequently seen in people who observe a solar eclipse without adequate protection and the mottled appearance of the macular region seen in camp amblyopia. They argue that "camp eyes" is a disease of undernourished people living in the tropics. Malnutrition of a similar degree must have prevailed occasionally in Europe, yet it did not produce camp eyes. In the regions from where camp eyes have been reported, the patients were subjected to strong sunlight, and the retinal damage may be attributable to the action of the tropical sun upon a tissue that has become sensitized to light by a dietary deficiency such as is present in pellagra. I believe that it is justifiable to argue similarly the case for optic neuritis, which can be regarded as due to a thiamine deficiency conditioned by known or unknown toxic factors.

Toxic Amblyopia

The nutritional amblyopia observed in the tropics and among prisoners of war seems to be closely related to the retrobulbar neuritis in alcohol and nicotine amblyopia (toxic amblyopia). Toxic amblyopia is considered to be the result of a toxic action of nicotine and alcohol on poorly nourished nerve cells, and it is possible to cure it by ensuring the patients an adequate diet or by giving them thiamine without depriving them of their habitual intake of alcohol or tobacco (58-60). The beneficial results of thiamine in toxic amblyopia have been confirmed frequently. As early as 1931, Keefer (61) suggested, from his observations of retrobulbar neuritis in Japan, that the occurrence of this condition in alcoholics should be investigated. Traquair (62) expressed the opinion that disturbances of the general nutrition played a part in the development of toxic retrobulbar neuritis. Jolliffe and co-workers (63) pointed out that every alcohol addict with polyneuritis has an inadequate intake of thiamine, and that alcohol in itself is not toxic to the central nervous system. The same attitude was taken by Fine and Lachman (64), and Johnson (65) reported excellent results of thiamine treatment in five alcohol-tobacco addicts in spite of continuation of alcohol and tobacco intake. Similar results have been reported by Gottlieb (66) and Shapiro (67).

It seems to be generally accepted that these results point to thiamine deficiency being the essential factor in the pathogenesis of toxic retrobulbar neuritis. Alcohol addicts often consume amounts of alcohol sufficient to lower the vitamin/calory ratios significantly. A smaller consumption of vitamin-containing food, and impaired absorption or utilization of the vitamin, are additional factors leading to vitamin deficiency in these subjects (68, 69). In alcoholism the organism is thus in a poor state of nutrition, particularly in regard to vitamins, and is more susceptible to the injurious action of poisons. Toxic amblyopia is another example of conditioning creating a vicious circle: alcohol abuse involves reduced thiamine intake which prepares the nerve cells for the action of nicotine and alcohol; at the same time impairment of the gastrointestinal functions reduces further the amount of utilizable thiamine. While the ultimate goal in the treatment of these patients is, of course, complete discontinuation of the abuse of intoxicants and tobacco, serious nervous complications can be prevented by the prompt institution of adequate dietary and vitamin therapy. There is an antagonism between this school of thought and another which claims equally good results in the treatment of toxic amblyopia with vaso-dilators (acetylcholine, sodium nitrate) (70-74). In view of the evidence available now it seems that it is quite possible to reconcile these opinions. It is likely that the basic cause of the condition is a nutritional disturbance, which can be symptomatically relieved by vaso-dilators.

Vitamin B complex and thiamine have also been used frequently and with good results in the treatment of retrobulbar neuritis of unknown origin (75-79). Although benefit might be expected from thiamine even in cases of toxic or infectious diseases of the optic nerve, the role of thiamine in these conditions is not yet very well understood.

Another instance of a conditioned affection of the optic nerve is the retrobulbar neuritis occasionally encountered in pregnancy (80-82). Hyperemesis gravidarum, impairing the vitamin intake, and increased vitamin requirement in pregnancy are probably the conditioning factors, and thiamine has been used with benefit in this condition.

A paper by Moore and Woods (83) on the pathology of syphilitic optic nerve atrophy should be mentioned here. They arrived at the conclusion that the most likely pathogenetic mechanism of this condition is a combination of neuro-syphilis and a nutritional deficiency of vitamin A. Their reasoning is based on excellent experimental and theoretical evidence. The suspected importance of vitamin A in the causation of retrobulbar neuritis in malnourished inhabitants of the tropics and in "camp eyes" has been mentioned before. Some stimulating work on the influence of vitamin A deficiency on the embryonal development of the eyes in experimental animals will be discussed later. On the basis of this work, Moore and Woods ascribe a definite place to vitamin A deficiency in the pathogenetic mechanism of syphilitic optic nerve atrophy, and this seems to be another striking example of an affection conditioned by vitamin deficiency. In this connection it may be interesting to mention an observation by Bergeret et al. (104) of a severe avitaminosis A in a case of syphilitic diffuse hepatitis with hypoplasia of the Kupffer system and very little vitamin A in the liver.

Pathology

There is scanty information available concerning the anatomical changes in the optic nerves of thiamine deficient animals. Co-carboxylase is the di-phosphoric acid ester of thiamine. This co-enzyme is important in the oxidation of pyruvic acid in the nerve tissues. It is believed that a lack of thiamine results in accumulation of pyruvic acid in the nerve tissue, with resulting anatomical and functional manifestations. It must be said, however, that there is no proof that the damage is really due to any toxic action of pyruvic acid. The optic nerve of thiamine deficient pigeons with beriberi shows edema and interruptions of the myelin sheath (84). Degeneration of the myelin sheath manifests itself by the formation of lipoid granules, particularly in the papillo-macular bundle, according to Marchesini and Papagno (85). These findings could, however, not be confirmed by Fazio (86).

The effect of vitamin A deficiency on the peripheral nerves (trigeminal) has been mentioned previously in the discussion on xerophthalmia. The first evidence that this vitamin is necessary for normal functioning of the nerve tissue was presented as early as 1929 by Hughes et al. (87). They found that young pigs fed on a vitamin A deficient diet from the time of weaning became blind after 6-10 months and developed incoordination and spasms. Degenerative changes in the optic, sciatic and femoral nerves were found in these animals. Pigs whose mothers are fed with a diet deficient in vitamin A during pregnancy are born with anophthalmos or microphthalmos (88, 89). Similar observations have been made on calves (90) and rats (91, 92, 105). These conditions are attributed to a malformation of the optic nerve, either primary (90, 93) or due to a stenosis of the optic canal (94). Mellanby (95) found degeneration in the chord, the 8th nerve and in some cases of the optic nerve in young dogs on a diet deficient in vitamin A. In one animal maintained on such a diet for 7 years the ganglion cell layer of the retina had completely disappeared and the optic nerve was replaced by a strand of connective tissue. Optic nerve degeneration was also observed in vitamin A deficient rats (96). Rats on a vitamin A deficient diet showed much more serious degenerative changes in the optic nerve when exposed to various poisons and bacteria than normal rats or those on a vitamin B complex deficient diet (97).

Prevalence

These findings are interesting and important; however, in the words of C. A. Elvehjem (98), "we must not underestimate the significance of the knowledge which has accumulated from histological studies on deficiencies, but I believe that these studies alone have not allowed us to elucidate the exact mechanism of vitamin activity."

It must also be pointed out that the experimental animals used in the investigations described were on severely restricted diets. Vitamin A deficient animals whose litters were born with malformations of the eyes had vitamin A serum levels of 1/10 or less of the normal (105). Such extremely low levels are not likely to occur in man, but it can not be excluded that less severe deficiencies may cause less severe changes, and further investigations must show what, if any, significance these findings have for human pathology.

Wernicke's Syndrome

In Wernicke's syndrome an ophthalmoplegia is observed, associated with clouding of consciousness, ataxia and other evidences of central nervous system involvement. The basic pathology of this syndrome consists of small foci of degeneration, varicose deformities of the blood vessels and petechial hemorrhages in the cerebral cortex and the region of the nuclei of the third, fourth and sixth cranial nerves. The etiology of the syndrome is complicated, but thiamine deficiency seems to be the cause of the ophthalmoplegia, and thiamine administration cures it promptly (99-103).

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VITAMIN K IN OPHTHALMOLOGY

Vitamin K is required by the organism for the formation of prothombin. In its absence the coagulation of the blood is disturbed. Vitamin K deficiency on a dietary basis is unknown in man because sufficient quantities are synthesized in the intestines by the intestinal flora and absorbed. Only when this absorption is disturbed, as in obstructive jaundice, liver diseases and disturbances in fat absorption does a secondary avitaminosis occur. The good results of vitamin K therapy in hemorrhagic conditions caused by these disturbances encouraged a number of workers to try it in ocular hemorrhages of various etiology. The outcome of these therapeutic trials is, unfortunately, not convincing.

The prophylatic use of vitamin K has been recommended to prevent hemorrhage in the new-born, where the intestinal flora is not yet established and a physiologically low prothrombin level exists. Maumenee, Hellman and Shattler (1), in a series of investigations concerning the factors influencing prothrombin in the new-born infant, examined the effect of antenatal administration of vitamin K on the incidence of retinal hemorrhages. They stated that the frequency of retinal hemorrhage in the new-born is reduced when vitamin K is administered to the mother just before the onset of labor. Wille (9) came to the same conclusion. Falls and Jurow (2) re-examined the question systematically and arrived at the opposite conclusion. Although vitamin K, given ante partum, raises the prothrombin level during its physiological decline, its administration before or during labor did not reduce the incidence of retinal hemorrhage in a consecutive series of 422 new-born. Belmonte Gonzales (10) agrees that a prothrombin deficiency is at least a predisposing cause in the production of retinal hemorrhages in the new-born (the main cause being the mechanical factor of the birth trauma). He denies, however, that antenatal administration of vitamin K to the mother is able to influence this physiological prothrombin deficiency.

Vitamin K has been tried also in certain other conditions involving intra-ocular hemorrhages. Burch and Meade (3) treated recurrent hemorrhagic retinitis and found that their cases improved under vitamin K therapy. Longhena (4) examined a number of patients with intra-ocular hemorrhages which did not present hypo-prothrombinemia and saw definite improvement with vitamin K in spite of the fact that these cases displayed normal coagulation time.

Vitamin K has been recommended for the prevention of post-operative hemorrhage. Kronfeld (5) pointed out that, in his experience, vitamin K is beneficial in this respect, even if the coagulation time of the patients is normal. His patients suffered post-operative hemorrhage less frequently if vitamin K had been administered before the operation. The same opinion was expressed by Kirby (6), who recommended pre-operative administration in patients undergoing cataract extraction, and by Azarova (11). Foss (7) failed, however, to find a connection between vitamin K and bleeding after surgery. De Voe (8) goes further and denies that vitamin K has any influence on the occurrence of post-operative hemorrhage after cataract extraction. The small number of publications and the inconclusive balance of the total of opinions points to the necessity of further systematic study.

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CENTRAL NERVOUS SYSTEM

In the course of our discussions it has been pointed out repeatedly how subclinical nutritional disorders may be responsible for disturbances of the visual apparatus. Subclinical vitamin deficiencies may condition the eye for the action of endogenous or exogenous noxious influences, and vice versa. The establish-ment of an adequate nutritional environment for the individual is essential for the maintenance of optimum performance of all vital functions. In addition to the clearcut deficiency states and syndromes described in the foregoing sections, there are many instances of degenerative disease of the vascular system and of metabolic disorders which affect the nutrition of the eye and its nervous centers, thus causing visual disturbances. But even in the absence of definite disease, we are aware that nutritional inadequacies may play a part in functional upsets of the visual apparatus.

Central nervous system fatigue is the most common and most important type of fatigue encountered in modern industry (1). Disturbances of vision may be the earliest detectable sign of such fatigue. The power of accommodation seems to suffer in malnutrition involving a deficiency of thiamine, and this vitamin or vitamin B complex is beneficial in many cases. This is understandable in the light of Sysi's investigations, who found that even normal, healthy subjects experienced an increase in the power of accommodation after the injection of 25-100 mgm. thiamine (2). These findings were confirmed by Knape (3) with even smaller doses (5 mgm.).

Similarly the fusion frequency of flicker, which is the frequency at which successive light flashes produce the sensation of plain light instead of flicker, is disturbed in nervous fatigue and can be improved by thiamine administration (4).

Improvement of color vision has also been claimed after administration of thiamine to normal persons (5).

It is necessary to proceed with great caution in these regions where extravagant claims have been made and freely popularized. Addition of vitamin

B complex or thiamine to the diet of healthy, normal children fails to influence growth, learning or vision (6). This has been established in experiments on 36 twins under careful controlled conditions.

Much critical work is required to clear up the important and largely unknown relations between malnutrition and the functions of the central nervous system. In using the fusion frequency of flicker and the power of accommodation as objective tests for fatigue, we will be in a position to make practical studies on the relation of nutritional status to resistance to, and recovery from, fatigue.

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VITAMIN P, HESPERIDIN, RUTIN IN OPHTHALMOLOGY

A group of substances closely related to each other chemically and of very similar characteristics biologically has attracted attention recently. Vitamin P occurs in lemon concentrates and has been found to have an effect on excessive permeability of capillaries. It is not a simple substance but an isomorphous mixture of hesperidin and another glucoside. Rutin is a glucoside which is chemically and pharmacologically very similar to hesperidin.

All these substances have been used in various hemorrhagic conditions of the eye, and a short review of the present state of knowledge may be in place here.

Matthewson (1) tried vitamin P in two cases of intra-ocular hemorrhages. One patient was receiving X-ray treatment for multiple myelomata and exhibited hemorrhages in the eye as well as elsewhere, the second one had undergone a cataract extraction followed by a hyphema. The hemorrhages not only did not recur but the ocular hemorrhages absorbed very satisfactorily after vitamin P administration. Mata (2) recommended vitamin P in hemorrhagic retinopathy of nephritic origin, juvenile recurrent hemorrhages and other extensive retinal hemorrhages. He suggested that it should be given together with vitamin C of which it is a complementary factor. Saubermann (3) treated unsuccessfully a case of thrombosis of the central retinal vein and another one of a fresh retinal periphlebitis with 80 mgm. of Neohesperidin daily. The unexpected result, however, was that in both second eyes of the patients, which had suffered from the same disease several years previously and which were showing now retinitis proliferans, the visual acuity was considerably improved. The same effect was observed in a case of Coats' disease, where the visual acuity improved without alteration of the ophthalmoscopic picture. Finally, Peck and Mann (4) could observe an improvement of the petechial index with vitamin P in many cases of diabetic retinopathy in which the prothrombin time was normal. The retinal hemorrhages, however, failed to change, nor did vitamin P influence the course of the condition.

Maclean and Brambel (5) believe rutin to be beneficial in recurrent retinal and vitreous hemorrhages.

They recommend a judicious concomitant use of anticoagulant drugs (heparin, dicumarol) and rutin or hesperidin in retinal vascular disorders like diabetic retinopathy, degenerative retinopathies etc. Shanno et al. (6) suggest on the basis of their therapeutic experiments with rutin on patients with retinal hemorrhages that an adequate dosage of rutin, given over a long enough period, may be of value in preventing further hemorrhages. Goedbloed (7) reported normalization of the increased fragility of the capillaries in two cases of arteriosclerotic or diabetic retinal hemorrhages, followed by the disappearance of the hemorrhages and improvement of the visual acuity.

These experiences are not shared by others. Levitt et al. (8) treated 12 patients with diabetic retinopathy exhibiting increased capillary fragility with 60 then 120 mgm. of rutin for three months. In eight cases they failed to find an improvement of the capillary fragility while two eyes showed definite improvement. One case showed a slight improvement of the capillary resistance, but the eyes deteriorated; two cases showed marked improvement of the capillary resistance and three eyes improved. A further case showed normalized capillary resistance while the retinopathy remained unchanged. The results of this experiment are representative of the unsettled state of affairs regarding the effect of rutin in such cases. Rodriguez and Root (9), working with a greater number of cases (156 diabetics altogether) could show that all diabetics with retinopathy exhibited increased capillary fragility. With 300-400 mgm. of rutin daily they were able to normalize the capillary fragility, but not one case of diabetic retinopathy improved clinically. Hollenhorst and Wagener (10) doubt that increased capillary fragility and permeability of the skin capillaries are accompanied by a corresponding dysfunction of the retinal capillaries, especially in diabetic retinopathy.

In glaucoma, an increased permeability of the capillary wall has been shown to be present in many cases. Stocker (11) has been able to show that rutin reduces this permeability, thereby enhancing the tension-reducing effect of miotics. Seventeen out of 26 eyes with chronic simple glaucoma were notably better controlled by miotics after 60 mgm. rutin had been given by mouth daily for 4 weeks; the effect seemed to be better still with 150 mgm. daily.

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In the continental literature of the past two decades a few scattered papers are concerned with an interesting effect of vitamin C which does not seem to have been followed up.

Bieling (1) found in 1927 that the lethal dose of diphtheria toxin is half of the normal in guinea pigs suffering from scurvy. According to Lereboullet (2) diphtheria serum is only effective if vitamin C is present in the organism, an opinion which has also been expressed by Lorentz (3) and Thaddea (4).

Bock and Grossmann (5) have verified this fact experimentally. Guinea pigs which received normal food and an additional 10—30 mgm. vitamin C per day showed less toxic signs when suffering from a diphtheric conjunctivitis than control animals not receiving the extra vitamin; and guinea pigs with diphtheric conjunctivitis exhibiting experimental scurvy showed a more markedly toxic reaction than normal controls.

These findings are given for what they are worth. It is, of course, not surprising that scurvy, and for that matter, any deficiency disease, decreases the resistance against infections. The protective action claimed for extra doses of vitamin C might be explained by a beneficial effect on the capillaries, preventing toxin absorption to a certain degree.

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NIACIN IN THE TREATMENT OF EYE CONDITIONS

In view of the small amount of factual knowledge on the role of vitamins in the organism at the disposal of the early workers, it is not surprising that vitamins have been tried in a great number of conditions which we know now are entirely unrelated to vitamin deficiencies. However, some vitamins have a pharmacological effect in addition to their physiological functions. The best example is the vasodilatory effect of niacin. The pharmacodynamic properties of vitamins have been exploited, and in the following lines the more interesting ones are mentioned.

Retinitis pigmentosa has been mentioned as occurring in pellagra by at least one authority (1), and retinal degeneration due to constriction of retinal vessels has also been observed (2). Pellagrins have been noted occasionally to present retinal homorrhages and white exudates (3). It seems to be doubtful whether there is a causal relation between niacin deficiency and retinal disease, but the vasodilatory effect of niacin has recommended it for treatment of retinitis pigmentosa all the same. Unfortunately, however, there is only scant evidence of beneficial results (4) while there seems to be no doubt in the minds of most investigators that this treatment is as much or as little use as that with other vasodilators like acetylcholine.

More promising seems to be the use of niacin in toxic affections of the optic nerve. Marconcini (5) poisoned rabbits with quinine, enucleated one eye when the poison had left its mark on the optic nerve, and treated the animal with niacin for ten days. While the first eye showed degeneration of the myelin sheaths, the second eye had recovered under niacin and almost complete regeneration of the myelin tissue was observed. However, similar results can be observed with the use of other vasodilators. Retrobulbar optic neuritis has been claimed to be favorably influenced by niacin (6).

Another theoretically interesting effect of the vasodilating action of niacin has been described by Simonelli (7). Niacin is present in the healthy lens and reduced in cataractous lenses. It is, however, unable to prevent the appearance of naphthalene cataract in rabbits. In fact, administration of niacin resulted in an acceleration of its appearance, and the author explains this on the basis of its vasodilating action, which increases the amount of the poison in the aqueous, and on a greater stimulation of the autooxidative processes of the lens. Niacin has also been used in the treatment of chronic glaucoma, together with other vasodilators, with interesting results by Gallois (8) and Monfette (9).

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SUBJECT INDEX.

AKNEPHASKOPIA 102
AMBLYOPIA
  nutritional
    vitamin B complex and 106
  toxic
    treatment with thiamine 110
    treatment with vasodilators 112
AMINO ACID
  deficiency
    cataracts and 82
    corneal vascularity in 40-42
ANAPHYLAXIS
  ocular
    treatment with vitamin C 71
AQUEOUS HUMOR
  ascorbic acid in 56 ff, 62 ff.
ARGININE
  see amino acid
ARIBOFLAVINOSIS
  see Riboflavin deficiency
ASCORBIC ACID
  in aqueous humor 56 ff, 62 ff.
  in cataract 65 ff, 76
  in diphtheritic conjunctivitis 126
  function in eye 57 ff.
  in lens 56 ff.
  in night blindness 92
  source in eye 58 ff.
  treatment with 54, 68-69, 71
  in treatment of cataract 68-69
  in treatment of central scotoma 71
  in treatment of Groenblad-Strandberg syndrome 71
  in treatment of keratitis 54
  in treatment of ocular anaphylaxis 71
  in treatment of ocular tuberculosis 71

BERIBERI
  optic symptoms of 106
BITOT'S SPOTS 2-3

CALCIUM
  in myopia 51-52
  in treatment of spring catarrh 48-49
CANTHI FISSURES
  in riboflavin deficiency 21
CARBOHYDRATE METABOLISM
  cataract and 85

CATARACT
  amino acid deficiency and 82
  ascorbic acid in 65 ff, 76
  in carbohydrate metabolism 85
  in diabetes mellitus 83-84
  experimental production of 77-79
  in galactosemia 85
  in histidine deficiency 83
  luminflavin in 75
  in phenylalanine deficiency 83
  riboflavin in 75-76
  sugars in 85-86
  treatment with ascorbic acid 68-69
  in tryptophane deficiency 83
  treatment with riboflavin 79
  vitamin B complex in 76 ff.

CHEILOSIS
  in riboflavin deficiency 20

CIRCUMCORNEAL INJECTION 19

COLOR VISION 103

CONJUNCTIVA 1
  in vitamin A deficiency 1-8
  Xerosis 1

CONJUNCTIVITIS
  diphtheritic
    ascorbic acid and 126
  follicular 4

CORNEA 1
  amino-acid deficiency in 40-42
  limbus 25
  vascularity 21, 25-26, 37
    in amino acid deficiency 40-42
    differential diagnosis 26
    etiology 16, 40
    experimental production of 32-33
    pathology 21, 41 ff.
    in phlyctenular kerato-conjunctivitis 27 ff.
    in protein deficiency 30
    in riboflavin deficiency 16, 18, 31 ff.
    in rosacea keratitis 26
    in sodium deficiency 31
    in thallium poisoning 31
    in trachoma 29
    treatment 35-36
    in zinc deficiency 31

CYSTINE
  function in lens 58 ff.

DARK ADAPTATION 88
  see also night blindness
  riboflavin in 102
  treatment with brewers' yeast 103

DIABETES MELLITUS
  cataract in 83-84

DIABETIC RETINOPATHY 104 ff.
  treatment with rutin 124
DIPHTHERITIC CONJUNCTIVITIS
  ascorbic acid and 126
DYSSEBACIA
  in riboflavin deficiency 21

FOLLICULAR CONJUNCTIVITIS 4

GALACTOSEMIA
  cataract and 85
GLAUCOMA
  treatment with rutin 125
GLOSSITIS
  in riboflavin deficiency 20
GLUTATHIONE
  function in lens 58 ff.
GROENBALD-STRANDBERG SYNDROME
  treatment with vitamin C 71

HEMERALOPIA 88
HESPERIDIN 122 ff.
HISTIDINE
  see also amino acid
  deficiency
    cataracts and 83

IRIS
  ascorbic acid in 61
ISOLEUCINE
  see amino acid

KERATITIS
  allergic eczematous
    in riboflavin deficiency 28
  herpetic
    treatment with thiamine 54
  in riboflavin deficiency 21
  treatment with ascorbic acid 54
  treatment with riboflavin 46
  treatment with vitamin E 45
KERATOCONUS
  etiology 44
  treatment with vitamin E 44
KERATOMALACIA 1, 3, 12
  treatment 14

LENS
  ascorbic acid in 56 ff.
  cystine in 57 ff.
  glutathione in 57 ff.
  physiology 56 ff.
  redox substances in 56 ff.

LEUCINE
  see amino acid
LIMBIC PLEXUS 25-26
LUMINFLAVIN
  in cataract 75
LYSINE
  see amino acid

METABOLIC PROCESS
  in eye 57 ff.
MELANIN PIGMENTATION
  in vitamin A deficiency 2
METHIONINE
  see amino acid
MYOPIA
  calcium in 51, 52
  vitamin D in 51

NEWFOUNDLAND
  Nutrition survey 7, 8
NIACIN (Niacinamide, Nicotinamide)
  in glaucoma 128
  in regeneration of vitamin A 91
  in retrobulbar neuritis 127
  in treatment of spring catarrh 48
  vasodilating action 127, 128
NIGHT BLINDNESS
  see also dark adaptation
  ascorbic acid in 92
  diagnosis 98
  etiology 88
  in liver disease 90
  pathology 96
  prevalence 96
  in retinal disease 88
  symptoms 88
  treatment 99, 102
  treatment with riboflavin 102
  vitamin A plasma level and 94, 97
NUTRITION SURVEY
  in Newfoundland 7-8
NYCTALOPIA 88

OCULAR HEMORRHAGE
  treatment with vitamin K 118, 119
OPHTHALMOPLEGIA
  in Wernicke's Syndrome 115
OPTIC NERVE
  pathology
  in thiamine deficiency 113
  vitamin A and 110-113
  in vitamin A deficiency 108, 112
  vitamin B complex and 114
  106-107, 109, 112

- PELLAGRA
  - eye signs in 16-17
  - retinitis pigmentosa in 127
- PERLECHE
  - in riboflavin deficiency 20
- PHENYLALANINE
  - see also amino acid
  - deficiency
    - cataracts and 83
- PHLYCTENULAR KERATO-CONJUNCTIVITIS
  - corneal vascularity in 27
  - treatment with riboflavin 27 ff.
- PINGUECULAE 5
- PORPHYROPSIN 89
- PROTEIN
  - deficiency
    - corneal vascularity in 30
- PROTHROMBIN
  - deficiency 119

- RECOMMENDED DIETARY ALLOWANCES
  - Vitamin A 13
- RETINA
  - night blindness in diseases of 88
- RETINAL HEMORRHAGE
  - treatment with rutin 123
  - treatment with vitamin P 123
  - vitamin K deficiency and 119
- RETINENE 89
- RETINITIS PIGMENTOSA
  - in pellagra 127
- RETINOPATHY
  - solar 109
- RETROBULBAR NEURITIS
  - conditioning factors of 109
  - treatment with niacin 127
  - treatment with thiamine 112
  - treatment with vitamin A 108
  - treatment with vitamin B complex 107, 112
  - vitamin A deficiency and 112
  - vitamin B complex and 109
- RHODOPSIN 89
- RIBOFLAVIN
  - anti-histaminic properties 48
  - in cataract 75-76, 79
  - in dark adaptation 102
  - deficiency 16
    - corneal vascularization in 16-18, 21, 25-26, 31 ff.
    - differential diagnosis 24, 31 ff.
    - experimental production 19, 22
    - keratitis 21, 28
    - pathology 21

        - riboflavin content of cornea 22-23
        - symptoms 17, 18, 19, 20
        - treatment 35, 36
    - function in cornea 21-23
    - in night blindness 91
    - treatment with 36, 53
    - in treatment of cataract 79
    - in treatment of corneal diseases 53
    - in treatment of interstitial keratitis 46
    - in treatment of phlyctenular kerato-conjunctivitis 27 ff.
    - treatment of rosacea keratitis with 27
    - in treatment of spring catarrh 47
    - in visual process 101-103
- Rosacea Keratitis
    - corneal vascularization in 26
    - treatment with riboflavin 27
- Rutin 122 ff.
    - in diabetic retinopathy 124
    - in glaucoma 125

- Sclera 1
- Scleral Rickets 51
- Scotoma, Central
    - treatment with ascorbic acid 71
- Scurvy
    - manifestations in eye 71
- Sjogren's Syndrome 49
- Sodium
    - deficiency
        - corneal vascularization in 31
- Spring Catarrh
    - treatment with calcium 48-49
    - treatment with niacinamide 48
    - treatment with riboflavin 47
    - treatment with vitamin D 49
- Stomatitis, Angular
    - in riboflavin deficiency 20
- Sugars
    - in cataracts 85, 86

- Thallium Poisoning
    - corneal vascularization in 31
- Thiamine
    - accommodation and 121
    - color vision and 121
    - deficiency
        - fusion frequency of flicker 121
        - ophthalmoplegia in 115
        - optic nerve 113
        - toxic neuritis 110
        - toxic retrobulbar neuritis in 111
    - treatment with 54

THREONINE
  see amino acid
TOXIC RETROBULBAR NEURITIS
  thiamine deficiency in 111
TRACHOMA
  corneal vascularization in 29
TRACHOMATOUS PANNUS 29 ff.
TRYPTOPHANE
  see also amino acid
  deficiency
    cataracts and 83
    signs 83
TUBERCULOSIS
  ocular
    treatment with ascorbic acid 71

VALINE
  see amino acid
VISUAL PROCESS
  riboflavin in 101-103
  vitamin A in 89
VISUAL PURPLE
  vitamin A and 89
VITAMIN A
  blood levels 10
  deficiency 1
    Bitot's Spots 2-4
    in conjunctiva 1-7, 11
    in cornea 1, 3
    corneal vascularization 8
    diagnosis 6, 12, 98
    etiology 90
    experimental production 7, 10-11, 92 ff., 114
    follicular conjunctivitis 4
    keratomalacia 3
    liver disease 1
    melanin pigmentation in 2
    in Newfoundland 7-8
    night blindness 88, 96
    optic nerve 114
    pathology 8-10, 96
    prevalence 12, 97
    in retrobulbar neuritis 108, 112
    in sclera 1
    symptoms 1-8, 88, 94, 96, 112, 114
    treatment 5, 13-14, 99
    xerosis conjunctivae 1
  and nicotinamide in vitamin A regeneration 91
  plasma level
    in night blindness 94, 97
    vitamin A intake and 94
  Recommended Dietary Allowances 13
  requirement of 13
  in retina 95

  storage in liver 92, 95
  in treatment of night blindness 99
  in treatment of retrobulbar neuritis 108
  in visual process 89
  visual purple and 89

VITAMIN A2 89

VITAMIN B COMPLEX
  deficiency of
    in cataract .... 76 ff.
    retrobulbar neuritis 107, 112
  in nutritional amblyopia 106
  in treatment of retrobulbar neuritis 107

VITAMIN B2
  see riboflavin and vitamin B complex

VITAMIN C
  see ascorbic acid

VITAMIN D
  in myopia 51-52
  in treatment of spring catarrh 49

VITAMIN E
  in treatment of interstitial keratitis 45
  in treatment of keratoconus 44

VITAMIN G
  see vitamin B complex and riboflavin

VITAMIN K
  in treatment of ocular hemorrhages 118, 119

VITAMIN P .... 122 ff.

WERNICKE'S SYNDROME 115

XEROPHTHALMIA 12

XEROSIS CONJUNCTIVAE 1, 12

ZINC
  deficiency
    corneal vascularization in 31

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